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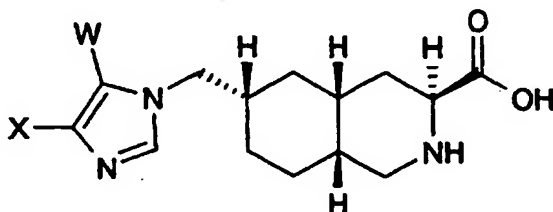
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WO 01/46173 A1

(54) Title: SELECTIVE iGLUR₁ RECEPTOR ANTAGONISTS



(I)

(57) Abstract: The present invention provides compounds of formula (I): wherein W represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂H, or CO₂H; and X represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂H, or CO₂H; with the proviso that at least one of W or X must be other than hydrogen; or a prodrug or a pharmaceutically acceptable salt thereof; which are useful for treating migraine.

SELECTIVE iGLUR₅ RECEPTOR ANTAGONISTS

In the mammalian central nervous system (CNS), the transmission of nerve impulses is controlled by the interaction between a neurotransmitter, that is released by a sending neuron, and a surface receptor on a receiving neuron, which causes excitation of this receiving neuron. L-Glutamate, which is the most abundant neurotransmitter in the CNS, mediates the major excitatory pathways in mammals, and is referred to as an excitatory amino acid (EAA). The receptors that respond to glutamate are called excitatory amino acid receptors (EAA receptors). See Watkins & Evans, *Ann. Rev. Pharmacol. Toxicol.*, 21, 165 (1981); Monaghan, Bridges, and Cotman, *Ann. Rev. Pharmacol. Toxicol.*, 29, 365 (1989); Watkins, Krogsgaard-Larsen, and Honore, *Trans. Pharm. Sci.*, 11, 25 (1990). The excitatory amino acids are of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiration, cardiovascular regulation, and sensory perception.

Excitatory amino acid receptors are classified into two general types. Receptors that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic." This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists *N*-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainic acid (KA). Molecular biological studies have established that AMPA receptors are composed of subunits (GluR₁ – GluR₄), which can assemble to form functional ion channels. Five kainate receptors have been identified which are classified as either High Affinity (KA1 and KA2) or Low Affinity (GluR₅, GluR₆, and GluR₇). Bleakman et al., *Molecular Pharmacology*, 49, No.4, 581,(1996).

The second general type of receptor is the G-protein or second messenger-linked "metabotropic" excitatory amino acid receptor. This second type is coupled to multiple second messenger systems that lead to enhanced phosphoinositide hydrolysis, activation of phospholipase D, increases or

decreases in cAMP formation, and changes in ion channel function. Schoepp and Conn, *Trends in Pharmacol. Sci.*, 14, 13 (1993). Both types of receptors appear not only to mediate normal synaptic transmission along excitatory pathways, but also to participate in the modification of synaptic connections during development and throughout life. Schoepp, Bockaert, and Sladeczek, *Trends in Pharmacol. Sci.*, 11, 508 (1990); McDonald and Johnson, *Brain Research Reviews*, 15, 41 (1990).

The excessive or inappropriate stimulation of excitatory amino acid receptors leads to neuronal cell damage or loss by way of a mechanism known as excitotoxicity. This process has been suggested to mediate neuronal degeneration in a variety of neurological disorders and conditions. The medical consequences of such neuronal degeneration makes the abatement of these degenerative neurological processes an important therapeutic goal.

Excitatory amino acid excitotoxicity has been implicated in the pathophysiology of numerous neurological disorders. For example, excitotoxicity has been linked with the etiology of cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord lesions resulting from trauma or inflammation, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage. In addition, excitotoxicity has been implicated in chronic neurodegenerative conditions including Alzheimer's Disease, Huntington's Chorea, inherited ataxias, AIDS-induced dementia, amyotrophic lateral sclerosis, idiopathic and drug-induced Parkinson's Disease, as well as ocular damage and retinopathy. Other neurological disorders implicated with excitotoxicity and/or glutamate dysfunction include muscular spasticity, tremors, drug tolerance and withdrawal, brain edema, convulsive disorders including epilepsy, depression, anxiety and anxiety related disorders such as post-traumatic stress syndrome, tardive dyskinesia, and psychosis related to depression, schizophrenia, bipolar disorder, mania, and drug intoxication or addiction. In addition, it has also been reported that excitatory amino acid excitotoxicity participates in the etiology of acute and chronic pain states including severe pain, intractable pain, neuropathic pain, and post-traumatic pain.

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The use of a neuroprotective agent, such as an excitatory amino acid receptor antagonist, is believed to be useful in treating or preventing these disorders and/or reducing the amount of neurological damage associated with these disorders. Excitatory amino acid receptor antagonists may also be useful
5 as analgesic agents.

Early theories regarding the pathophysiology of migraine have been dominated since 1938 by the work of Graham and Wolff (*Arch. Neurol. Psychiatry*, 39, 737-63 (1938)). They proposed that the cause of migraine headache is vasodilatation of extracranial vessels. This view is supported by
10 knowledge that ergot alkaloids and sumatriptan contract cephalic vascular smooth muscle and are effective in the treatment of migraine. Sumatriptan is a hydrophilic agonist at the serotonin 5-HT₁-like receptors and does not cross the blood-brain barrier (Humphrey, et al., *Ann. NY Acad. Sci.*, 600, 587-600 (1990)). Consequently, several series of compounds said to be useful for the treatment of
15 migraine, have been developed to optimize the 5-HT₁-like mediated vasoconstrictive activity of sumatriptan. However, sumatriptan's contraindications, including coronary vasospasm, hypertension, and angina are also products of its vasoconstrictive activity (MacIntyre, P.D., et al., *British Journal of Clinical Pharmacology*, 34, 541-546 (1992); Chester, A.H., et al.,
20 *Cardiovascular Research*, 24, 932-937 (1990); Conner, H.E., et al., *European Journal of Pharmacology*, 161, 91-94 (1990)).

While the vascular mechanism for migraine has gained wide acceptance, there is not total agreement as to its validity. Moskowitz, for example, has shown the occurrence of migraine headaches, independent of changes in vessel
25 diameter (*Cephalalgia*, 12, 5-7, (1992)). It is known that the trigeminal ganglion, and its associated nerve pathways, are associated with painful sensations from the face such as headache, in particular migraine. Moskowitz proposed that unknown triggers stimulate the trigeminal ganglia which innervate vasculature within cephalic tissue, giving rise to the release of vasoactive neuropeptides from
30 axons innervating the vasculature. These neuropeptides initiate a series of events leading to neurogenic inflammation of the meninges, a consequence of which is pain. This neurogenic inflammation is blocked by sumatriptan at doses

similar to those required to treat acute migraine in humans. However, such doses of sumatriptan, as stated, are associated with contraindications as a result of sumatriptan's attendant vasoconstrictive properties.(see *supra*.)

5 5-HT_{1D} receptors have been implicated as mediating the blockade of neurogenic protein extravasation. (*Neurology*, 43(suppl. 3), S16-S20 (1993)). In addition, it has been reported that α_2 , H₃, m-opioid and somatostatin receptors may also be located on trigeminovascular fibers and may block neurogenic plasma extravasation (Matsubara *et al.*, *Eur. J. Pharmacol.*, 224, 145-150 (1992)). Weinshank *et al.* have reported that sumatriptan and several ergot
10 alkaloids have a high affinity for the serotonin 5-HT_{1F} receptor, suggesting a role for the 5-HT_{1F} receptor in migraine (WO93/14201).

European Patent Application Publication No. 590789A1 and United States Patents No. 5,446,051 and 5,670,516 disclose that certain decahydroisoquinoline derivative compounds are AMPA receptor antagonists
15 and, as such, are useful in the treatment of many different conditions, including pain and migraine headache.

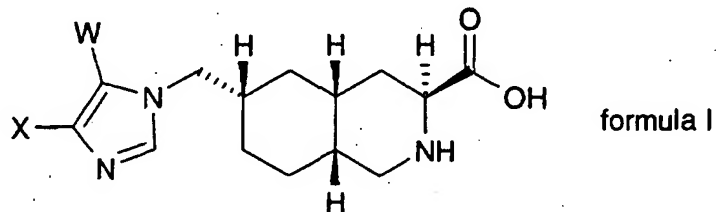
Recently, it has been reported that all five members of the kainate subtype, of ionotropic glutamate receptors, are expressed on rat trigeminal ganglion neurons. In particular, high levels of GluR₅ and KA2 have been
20 observed. (Sahara *et al.*, *The Journal of Neuroscience*, 17(17), 6611 (1997)). Simmons *et al.* reported that the kainate GluR₅ receptor subtype mediates the nociceptive response to formalin in a rat model of persistent pain.(*Neuropharmacology*, 37, 25 (1998)). Further, WO98/45270 previously disclosed that antagonists selective for the iGluR₅ receptor are useful for the
25 treatment of pain, including; severe, chronic, intractable, and neuropathic pain.

In accordance with the present invention, Applicants have discovered compounds that are antagonists of the iGluR₅ receptor subtype and which are surprisingly selective for the iGluR₅ receptor subtype. In addition, the compounds of the present invention are efficacious in an animal model of
30 neurogenic inflammation and, thus, could be useful for the treatment of migraine. Such selective antagonists could address a long felt need for a safe and

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effective treatment for migraine, without attending side effects. The treatment of neurological disorders is hereby furthered. Furthermore, the diester prodrugs of the corresponding diacids have been found to possess substantially improved bioavailability as compared to the corresponding diacids.

5 The present invention provides compounds of formula I:



wherein

W represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂H, or CO₂H; and

X represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂H, or CO₂H;

10 with the proviso that at least one of W or X must be other than hydrogen; or a prodrug or a pharmaceutically acceptable salt thereof.

The present invention further provides a method of treating migraine which comprises administering to a patient an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

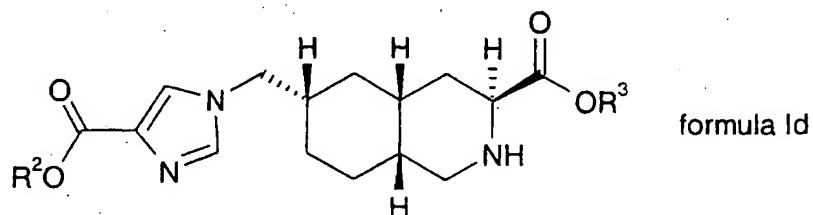
15 In another embodiment, the present invention provides a method of treating or preventing a neurological disorder, or neurodegenerative condition, comprising administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. Examples of such neurological disorders, or neurodegenerative conditions, include:

20 cerebral deficits subsequent to cardiac bypass surgery and grafting; stroke; cerebral ischemia; spinal cord lesions resulting from trauma or inflammation; perinatal hypoxia; cardiac arrest; hypoglycemic neuronal damage; Alzheimer's Disease; Huntington's Chorea; inherited ataxias; AIDS-induced dementia; amyotrophic lateral sclerosis; idiopathic and drug-induced Parkinson's Disease;

25 ocular damage and retinopathy; muscular spasticity, tremors; drug tolerance and withdrawal; brain edema; convulsive disorders including epilepsy; depression; anxiety and anxiety related disorders such as post-traumatic stress syndrome; tardive dyskinesia; psychosis related to depression, schizophrenia, bipolar

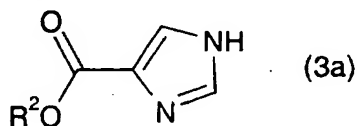
disorder, mania, and drug intoxication or addiction; and acute and chronic pain states including severe pain, intractable pain, neuropathic pain, and post-traumatic pain.

The invention further provides a process for preparing a compound of
 5 formula Id:

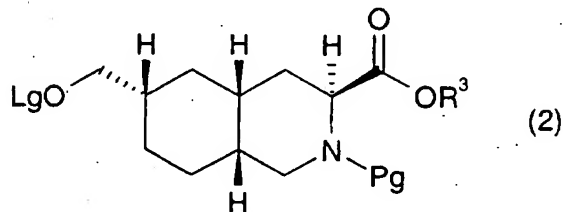


wherein

R^2 and R^3 each independently represent C_1 - C_{20} alkyl, C_2 - C_6 alkenyl,
 C_1 - C_6 alkylaryl, C_1 - C_6 alkyl(C_3 - C_{10})cycloalkyl, C_1 - C_6 alkyl-N,N- C_1 - C_6 dialkylamine,
 10 C_1 - C_6 alkyl-pyrrolidine, C_1 - C_6 alkyl-piperidine, or C_1 - C_6 alkyl-morpholine;
 comprising combining a compound of structure (3a):



wherein R^2 is defined as above, with a suitable base in a suitable solvent,
 followed by addition of a compound of structure (2):

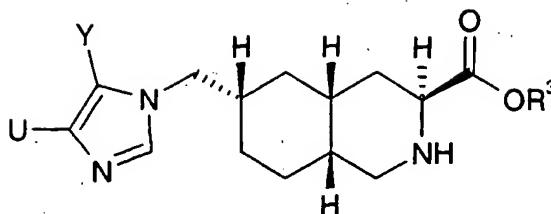


15

wherein R^3 is defined as above, Pg is a suitable nitrogen protecting group, and
 OLg is a suitable leaving group, followed by removal of the nitrogen protecting
 group.

The present invention further provides a compound of the formula:

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wherein

Y represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂R¹, or CO₂R¹;

U represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂R², or CO₂R²; and

- 5 R¹, R² and R³ each independently represent hydrogen, C₁-C₂₀ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkylaryl, C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl, C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine, C₁-C₆ alkyl-pyrrolidine, C₁-C₆ alkyl-piperidine, or C₁-C₆ alkyl-morpholine;

or a pharmaceutically acceptable salt thereof,

- 10 with the proviso that at least one of Y or U is other than hydrogen or C₁-C₄ alkyl, and with the further proviso that at least one of R¹, R² or R³ is other than hydrogen.

- In addition, the invention provides pharmaceutical compositions of compounds of formula I, including the hydrates thereof, comprising, as an active
15 ingredient, a compound of formula I in combination with a pharmaceutically acceptable carrier, diluent or excipient. This invention also encompasses novel intermediates, and processes for the synthesis of the compounds of formula I.

- According to another aspect, the present invention provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof as defined
20 hereinabove for the manufacture of a medicament for treating migraine.

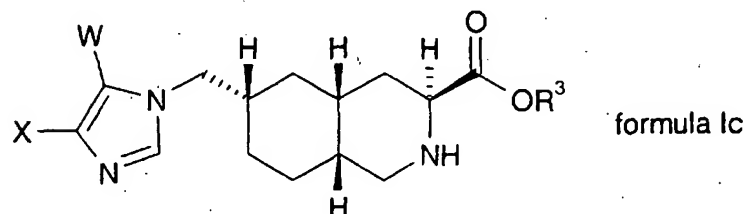
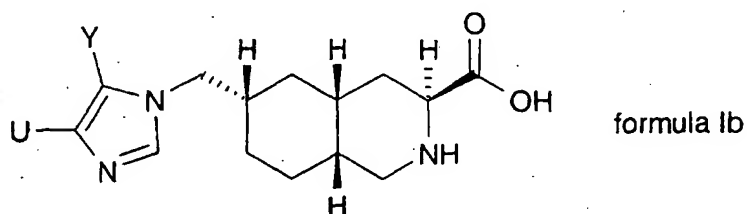
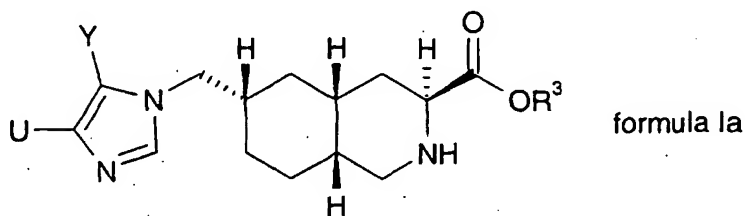
According to yet another aspect, the present invention provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinabove for treating migraine.

- The present invention provides a method for the treatment of migraine
25 which can be demonstrated by a particular mechanism of action, inhibition of neurogenic dural protein extravasation. By treating a migraineur with a compound of formula I which is a selective antagonist of the iGluR₅ receptor, the neurogenic extravasation which mediates migraine is inhibited without the

attending side effects of agents designed to optimize the 5-HT₁-like mediated vasoconstrictive activity of sumatriptan.

As used herein, the term "prodrug" refers to a compound of the formula I which has been structurally modified such that *in vivo* the prodrug is converted into the parent compound of the formula I (for example, by hydrolytic, oxidative, reductive, or enzymatic cleavage). Such prodrugs may be, for example, metabolically labile ester or amide derivatives of the parent compound having a carboxylic acid group. It is to be understood that the present invention includes any such prodrugs, such as metabolically labile ester or amide derivatives of compounds of the formula I. Conventional procedures for the selection and preparation of suitable prodrugs are well known to one of ordinary skill in the art.

More specifically, examples of prodrugs of formula I which are understood to be included within the scope of the present invention are represented by formulas Ia, Ib and Ic below:



15

wherein

W and X are as defined hereinabove;

Y represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂R¹, or CO₂R¹;

U represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂R², or CO₂R²; and
R¹, R² and R³ each independently represent hydrogen, C₁-C₂₀ alkyl, C₂-C₆
alkenyl, C₁-C₆ alkylaryl, C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl, C₁-C₆ alkyl-N,N-C₁-C₆
dialkylamine, C₁-C₆ alkyl-pyrrolidine, C₁-C₆ alkyl-piperidine, or C₁-C₆ alkyl-
5 morpholine;
with the proviso that at least one of Y or U is other than hydrogen or C₁-C₄ alkyl,
and with the further proviso that at least one of R¹, R² or R³ is other than
hydrogen.

As used herein, the terms "Me", "Et", "Pr", "iPr", "Bu" and "t-Bu" refer to
10 methyl, ethyl, propyl, isopropyl, butyl and tert-butyl, respectively.

As used herein, the terms "Halo", "Halide" or "Hal" refer to a chlorine,
bromine, iodine or fluorine atom, unless otherwise specified herein.

As used herein the term "C₁-C₄ alkyl" refers to a straight or branched,
monovalent, saturated aliphatic chain of 1 to 4 carbon atoms and includes, but is
15 not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and the like.

As used herein the term "C₁-C₆ alkyl" refers to a straight or branched,
monovalent, saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is
not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl,
n-hexyl, and the like.

20 As used herein the term "C₁-C₁₀ alkyl" refers to a straight or branched,
monovalent, saturated aliphatic chain of 1 to 10 carbon atoms and includes, but
is not limited to methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl,
pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-
methyl-2-hexyl, octyl, 4-methyl-3-heptyl and the like.

25 As used herein the term "C₁-C₂₀ alkyl" refers to a straight or branched,
monovalent, saturated aliphatic chain of 1 to 20 carbon atoms and includes, but
is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl,
isopentyl, hexyl, 3-methylpentyl, 2-ethylbutyl, n-heptyl, n-octyl, n-nonyl, n-decyl,
n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-
30 heptadecyl, n-nonadecyl, n-eicosyl and the like.

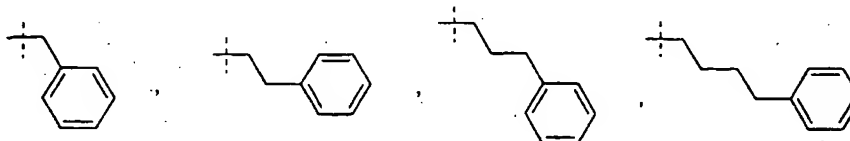
As used herein the term "C₁-C₆ alkoxy" refers to a straight or branched
alkyl chain having from one to six carbon atoms attached to an oxygen atom.

Typical C₁-C₆ alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and the like. The term "C₁-C₆ alkoxy" includes within its definition the term "C₁-C₄ alkoxy".

As used herein the term "C₂-C₆ alkenyl" refers to a straight or branched, monovalent, unsaturated aliphatic chain having from two to six carbon atoms. Typical C₂-C₆ alkenyl groups include ethenyl (also known as vinyl), 1-methylethenyl, 1-methyl-1-propenyl, 1-butenyl, 1-hexenyl, 2-methyl-2-propenyl, 1-propenyl, 2-propenyl, 2-butenyl, 2-pentenyl, and the like.

As used herein, the term "aryl" refers to monovalent carbocyclic group containing one or more fused or non-fused phenyl rings and includes, for example, phenyl, 1- or 2-naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and the like.

As used herein, the term "C₁-C₆ alkylaryl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an aryl group attached to the aliphatic chain. Included within the term "C₁-C₆ alkylaryl" are the following:

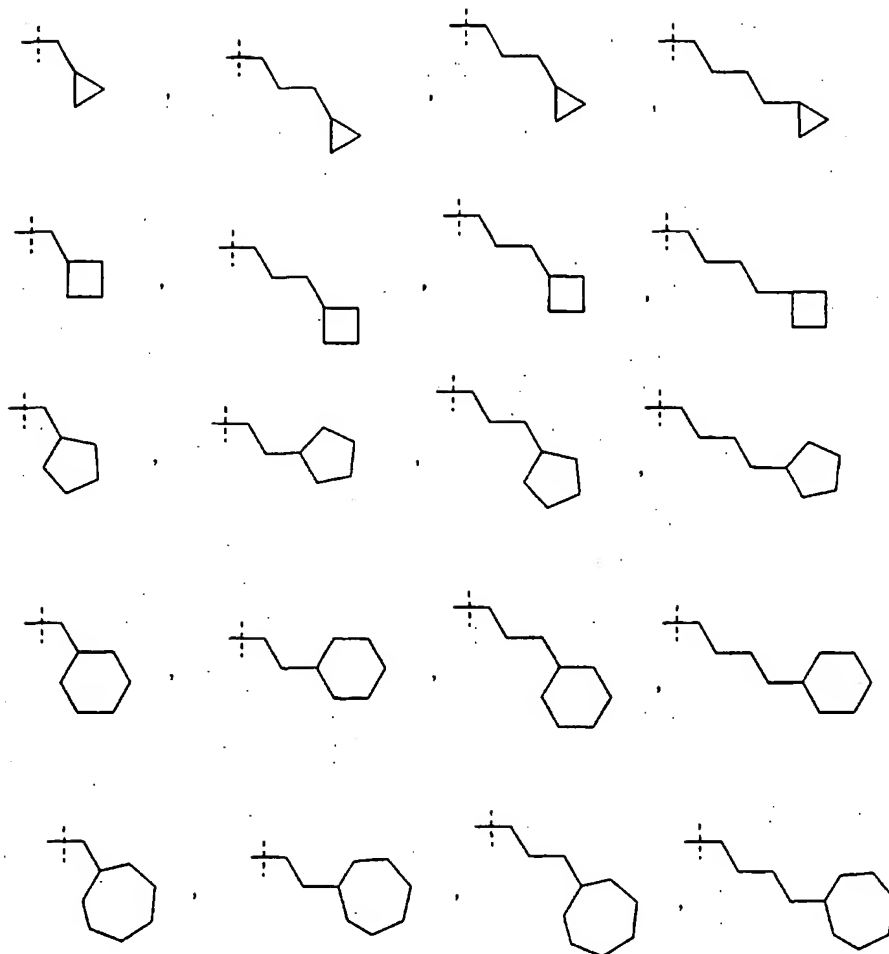


and the like.

As used herein the term "(C₃-C₁₀)cycloalkyl" refers to a saturated hydrocarbon ring structure containing from three to ten carbon atoms. Typical C₃-C₁₀ cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. It is understood that "(C₃-C₈)cycloalkyl" and "(C₄-C₆)cycloalkyl" is included within the term "(C₃-C₁₀)cycloalkyl".

As used herein, the term "C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a (C₃-C₁₀)cycloalkyl attached to the aliphatic chain. Included within the term "C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl" are the following:

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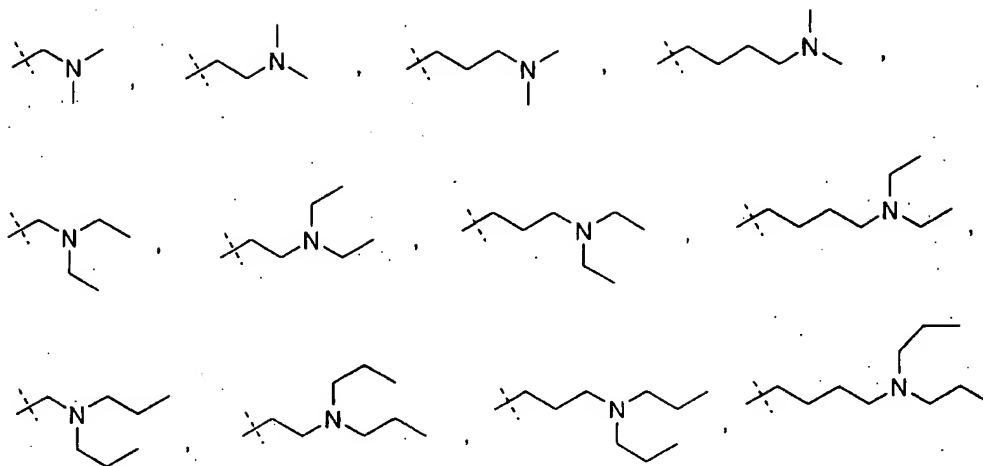


and the like.

As used herein the term "N,N-C₁-C₆ dialkylamine" refers to a nitrogen atom substituted with two straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms. Included within the term "N,N-C₁-C₆ dialkylamine" are -N(CH₃)₂, -N(CH₂CH₃)₂, -N(CH₂CH₂CH₃)₂, -N(CH₂CH₂CH₂CH₃)₂, and the like.

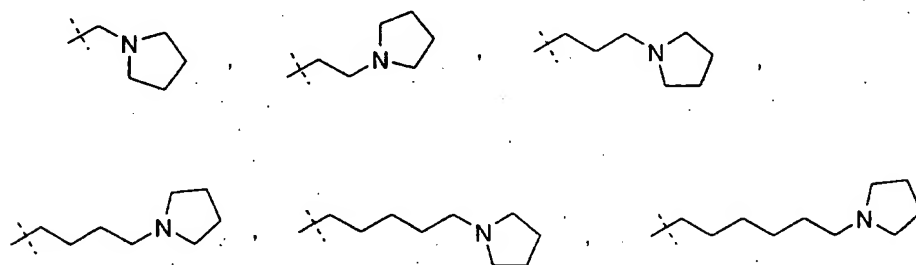
As used herein the term "C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine" refers to straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an N,N-C₁-C₆ dialkylamine attached to the aliphatic chain. Included within the term "C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine" are the following:

-12-



and the like.

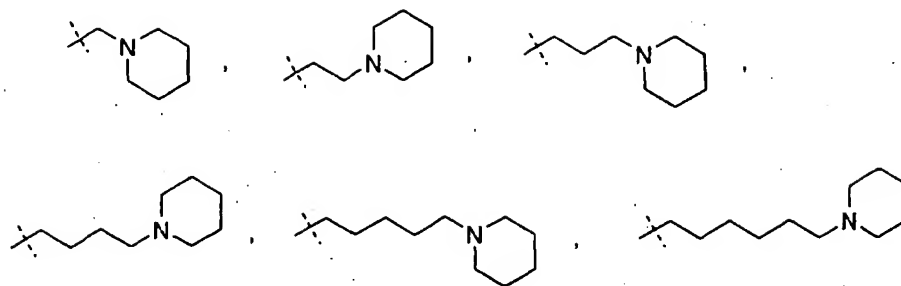
As used herein the term "C₁-C₆ alkyl-pyrrolidine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a pyrrolidine attached to the aliphatic chain. Included within the scope of the term "C₁-C₆ alkyl-pyrrolidine" are the following:



and the like.

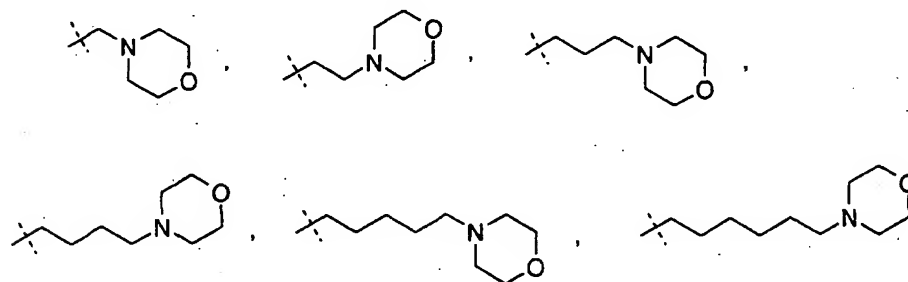
As used herein the term "C₁-C₆ alkyl-piperidine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a piperidine attached to the aliphatic chain. Included within the scope of the term "C₁-C₆ alkyl-piperidine" are the following:

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and the like.

As used herein the term "C₁-C₆ alkyl-morpholine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a morpholine attached to the aliphatic chain. Included within the scope of the term "C₁-C₆ alkyl-morpholine" are the following:



and the like.

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The designation "  " refers to a bond that protrudes backward out of the plane of the page.

As used herein the term "iGluR₅" refers to the kainate ionotropic glutamate receptor, subtype 5, of the larger class of excitatory amino acid receptors.

As used herein the term "migraine" refers a disorder of the nervous system characterized by recurrent attacks of head pain (which are not caused by a structural brain abnormality such as those resulting from tumor or stroke), gastrointestinal disturbances, and possibly neurological symptoms such as visual distortion. Characteristic headaches of migraine usually last one day and are commonly accompanied by nausea, emesis, and photophobia.

Migraine is a "chronic" condition. The term "chronic", as used herein, means a condition of slow progress and long continuance. As such, a chronic condition is treated when it is diagnosed and treatment is continued throughout the course of the disease. Conversely, the term "acute" means an exacerbated event or attack, of short course, followed by a period of remission. Thus, the treatment of migraine contemplates both acute events and chronic conditions. In an acute event, compound is administered at the onset of symptoms and discontinued when the symptoms disappear. As described above, a chronic condition is treated throughout the course of the disease.

10 It is understood that the term "selective iGluR₅ receptor antagonist" as used herein, includes those excitatory amino acid receptor antagonists which selectively bind to the iGluR₅ kainate receptor subtype, relative to the iGluR₂ AMPA receptor subtype. The selective iGluR₅ antagonist of formula I for use according to the method of the present invention has a binding affinity at least 20
15 fold greater for iGluR₅ than for iGluR₂.

This invention includes the hydrates and the pharmaceutically acceptable salts of the compounds of formula I. A compound of this invention can possess a sufficiently basic functional group which can react with any of a number of inorganic and organic acids, to form a pharmaceutically acceptable salt.

20 The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of formula I which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid. Such salts are also known
25 as acid addition salts. Such salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2-19 (1977) which are known to the skilled artisan.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic,
30 methanesulfonic acid, benzenesulfonic acid, oxalic acid, *p*-bromophenylsulfonic

acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, 5 propionate, decanoate, caprate, caprylate, acrylate, ascorbate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, propionate, phenylpropionate, salicylate, oxalate, malonate, succinate, suberate, sebacate, fumarate, malate, maleate, hydroxymaleate, mandelate, nicotinate, isonicotinate, cinnamate, hippurate, nitrate, phthalate, teraphthalate, butyne-1,4- 10 dioate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, dinitrobenzoate, *o*-acetoxybenzoate, naphthalene-2-benzoate, phthalate, *p*-toluenesulfonate, *p*-bromobenzenesulfonate, *p*-chlorobenzenesulfonate, xylenesulfonate, phenylacetate, trifluoroacetate, 15 phenylpropionate, phenylbutyrate, citrate, lactate, α -hydroxybutyrate, glycolate, tartrate, benzenesulfonate, methanesulfonate, ethanesulfonate, propanesulfonate, hydroxyethanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, 1,5-naphthalenedisulfonate, mandelate, tartarate, and the like. Preferred pharmaceutically acceptable acid addition salts are those 20 formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid, oxalic acid and methanesulfonic acid.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a 25 whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. It is further understood that such salts may exist as a hydrate.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three- 30 dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror

images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

$$ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100$$

wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 50:30 is achieved, the ee with respect to the first enantiomer is 25%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art.

Some of the compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

The specific stereoisomers and enantiomers of compounds of formula I can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen, "Stereochemistry of Organic Compounds", (Wiley-Interscience 1994), and European Patent Application No. EP-A-838448, published April 29, 1998.

For example, the specific stereoisomers and enantiomers can be prepared by stereospecific syntheses using enantiomerically and geometrically pure, or enantiomerically or geometrically enriched starting materials. In addition, the specific stereoisomers and enantiomers can be resolved and recovered by techniques such as chromatography on chiral stationary phases, enzymatic resolution or fractional recrystallization of addition salts formed by reagents used for that purpose.

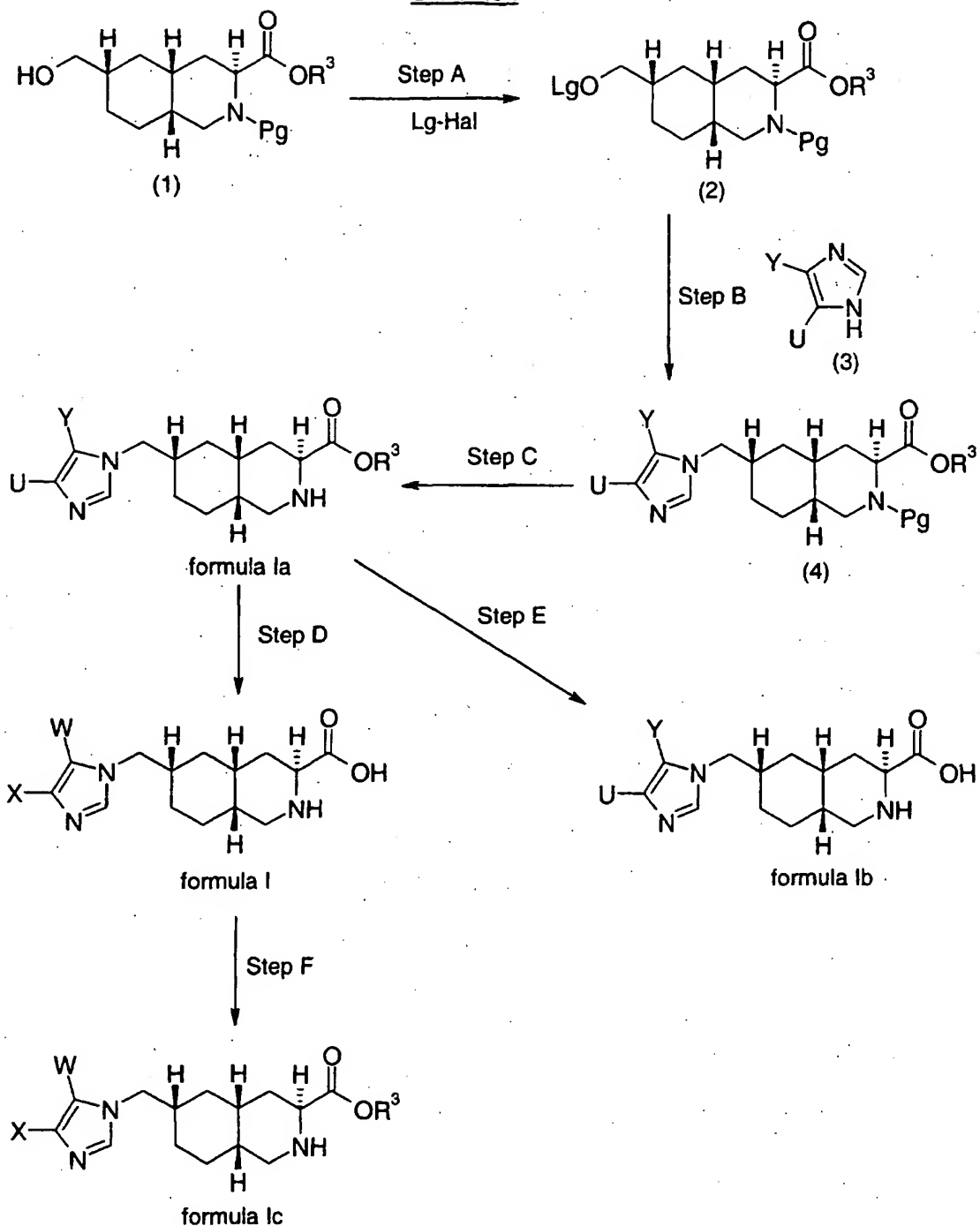
As used herein the term "Pg" refers to a suitable nitrogen protecting group. Examples of a suitable nitrogen protecting group as used herein refers to those groups intended to protect or block the nitrogen group against undesirable reactions during synthetic procedures. Choice of the suitable nitrogen protecting group used will depend upon the conditions that will be employed in subsequent reaction steps wherein protection is required, and is well within the knowledge of one of ordinary skill in the art. Commonly used nitrogen protecting groups are

disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)). Suitable nitrogen protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, .alpha.-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, .alpha.,.alpha.-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred suitable nitrogen protecting groups are formyl, acetyl, methyloxycarbonyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

Compounds of formula I can be prepared, for example, by following the procedures set forth in Scheme I. These schemes are not intended to limit the scope of the invention in any way. All substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art. For example, certain necessary starting materials can be prepared by one of ordinary skill in the art following procedures disclosed in U.S. Patent No. 5,356,902, issued October 18, 1994, J. Org. Chem., 56(14), 4388 (1991), and J. Org. Chem., 59, 7862 (1994).

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Scheme I



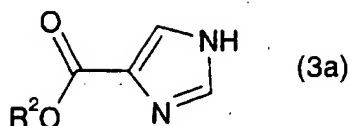
In Scheme I, step A, the compound of structure (1) is treated under
 5 standard conditions with a compound of formula Lg-Hal, wherein Lg is a suitable

leaving group and Hal represents a chloro, bromo or iodo atom, to provide the compound of structure (2). For example, compound (1) is dissolved in a suitable organic solvent, such as methylene chloride and treated with about 1 to 2 equivalents of a compound of formula Lg-Hal and an excess of a suitable organic base, such as triethylamine. Examples of Lg-Hal include m-nitrobenzenesulfonyl chloride, p-nitrobenzenesulfonyl chloride, p-bromobenzenesulfonyl chloride, p-toluenesulfonyl chloride, benzenesulfonyl chloride, methanesulfonyl chloride, trifluoromethanesulfonyl chloride, and the like. The reaction mixture is stirred for about 5 to 20 hours at a temperature of about 0°C to room temperature. The compound (2) is then isolated using standard procedures, such as extraction techniques. For example, the reaction mixture is washed with water, 1N aqueous HCl, saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, filtered and concentrated to provide compound (2).

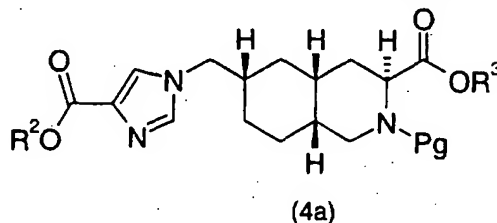
In Scheme I, step B, compound (2) is non-regioselectively alkylated with the imidazole of structure (3) to provide the compound of structure (4). For example, compound (3) is dissolved in an organic solvent, such as *N,N*-dimethylformamide, under an atmosphere of nitrogen, and added to about 1 to 1.2 equivalents of a base in *N,N*-dimethylformamide. The reaction mixture is then treated with compound (2) dissolved in *N,N*-dimethylformamide and the reaction is stirred at room temperature for about 10 to 20 hours. The reaction is then quenched and compound (4) is isolated and purified by standard techniques well known in the art. For example, the reaction is quenched with saturated aqueous sodium bicarbonate and the quenched reaction mixture is filtered. The filtrate is extracted with a suitable organic solvent, such as ethyl acetate, the organic extracts are combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to provide crude compound (4). This crude material is then purified by chromatography on silica gel with a suitable eluent, such as ethyl acetate or methanol/chloroform to provide purified compound (4).

Alternatively, in Scheme I, step B, compound (2) is regioselectively alkylated with the imidazole of structure (3a):

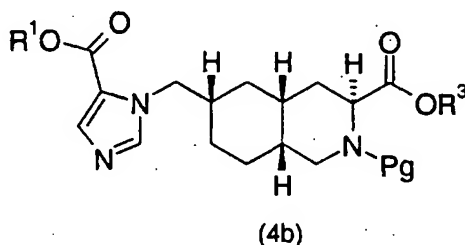
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to provide predominately the compound of structure (4a):



as opposed to the compound of (4b):



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For example, compound (3a) is combined with a suitable base in a suitable organic solvent, at a temperature of about 0°C to about 40°C with about 20°C being preferred. Examples of suitable organic solvents include tetrahydrofuran, 1,4-dioxane, diethyl ether, glymes, and the like, with tetrahydrofuran being preferred. Examples of suitable bases include sodium hydride, DBU, potassium carbonate, potassium tert-butoxide, and the like, with sodium hydride being preferred. The reaction mixture is stirred for about 0.5 hours to about 1.5 hours, with about 1 hour being preferred. This reaction mixture is then combined with a compound of structure (2) as defined above, at a temperature of about 0°C to about 40°C with about 20°C being preferred. The reaction mixture is allowed to stir for about 4 hours to about 40 hours with about 16 hours being preferred. The reaction is then quenched and compound (4a) is isolated and purified by standard techniques well known in the art. For example, the reaction is quenched with water and extracted with a suitable solvent, such as methylene chloride. The organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide crude (4a). This crude material is

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then purified by flash chromatography on silica gel with a suitable eluent, such as 5% to 10% ethanol/toluene containing 0.5% dimethylamine to provide purified compound of structure (4a).

In Scheme I, step C, compound (4) is deprotected under standard
5 conditions well known in the art to provide the compound of formula Ia. For example, when Pg is a methoxycarbonyl protecting group, compound (4) is dissolved in a suitable organic solvent, such as dry dichloromethane under an atmosphere of nitrogen, and treated with trimethylsilyl iodide at room temperature. The reaction mixture is stirred for about 10 to 20 hours. The
10 reaction is quenched and compound of formula Ia is isolated and purified using standard techniques well to known to one of ordinary skill in the art. For example, the reaction is quenched by addition of ethanol and then concentrated under vacuum. The residue is dissolved in a suitable organic solvent, such as ethyl acetate and the organic is rinsed with saturated sodium bicarbonate. The
15 aqueous layer is extracted with ethyl acetate. The organic extracts and organic layer are combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide crude compound of formula Ia. This crude material is then purified by chromatography on silica gel with a suitable eluent, such as methanol/chloroform to provide purified compound of
20 formula Ia.

In Scheme I, step D, the compound of formula Ia is hydrolyzed to the compound of formula I under conditions well known in the art. For example, compound of formula Ia is dissolved in a suitable organic solvent, such as methanol, and treated with an excess of a suitable base. Examples of suitable
25 bases include aqueous lithium hydroxide, sodium hydroxide, potassium hydroxide, and the like. Lithium hydroxide is preferred. The reaction is stirred for about 10 to 20 hours. The reaction mixture is then neutralized to pH 6 with 1 N HCl and concentrated under vacuum to provide crude compound of formula I. This crude material is then purified by techniques well known in the art, such as
30 cation exchange chromatography eluting with methanol/water followed by ammonium hydroxide/methanol to provide purified compound of formula I.

In Scheme I, step E, the compound of formula Ia is selectively hydrolyzed to provide the compound of formula Ib. For example, the compound of formula Ia is dissolved in 5 N aqueous HCl and heated at about 50°C for about 3 hours. It is then allowed to stir at room temperature for about 18 hours and the reaction
5 is concentrated under vacuum to provide crude compound of formula Ia. This crude material is purified by standard techniques well known to one of ordinary skill, for example by reverse phase chromatography on C18 modified silica gel with a suitable eluent, such as acetonitrile in aqueous 0.1% HCl to provide purified compound of formula Ib.

10 In Scheme I, step f, the compound of formula I is selectively esterified to provide the compound of formula Ic. For example, the compound of formula I is dissolved in a suitable organic solvent, such as ethanol and the solution is treated with 1M HCl in diethyl ether. The reaction is heated at reflux for about 8 to 12 hours, cooled, and concentrated under vacuum to provide crude compound
15 of formula Ic. This crude material is then purified by standard techniques well known in the art, for example by reverse phase chromatography on C18 modified silica gel with a suitable eluent, such as acetonitrile in aqueous 0.1% HCl to provide purified compound of formula Ic.

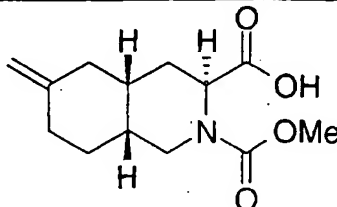
The following examples further illustrate the invention and represent
20 typical syntheses of the compounds of formula I as described generally above. The reagents and starting materials are readily available to one of ordinary skill in the art. As used herein, the following terms have the meanings indicated: "eq" or "equiv." refers to equivalents; "g" refers to grams; "mg" refers to milligrams; "L" refers to liters; "mL" refers to milliliters; "μL" refers to microliters;
25 "mol" refers to moles; "mmol" refers to millimoles; "psi" refers to pounds per square inch; "min" refers to minutes; "h" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ" refers to parts per million down-field from tetramethylsilane;
30 "THF" refers to tetrahydrofuran; "DMF" refers to *N,N*-dimethylformamide; "DMSO" refers to methyl sulfoxide; "LDA" refers to lithium diisopropylamide; "aq" refers to aqueous; "EtOAc" refers to ethyl acetate; "iPrOAc" refers to isopropyl

acetate; "MeOH" refers to methanol; "EtOH" refers to ethanol; "MTBE" refers to tert-butyl methyl ether, "tlc" refers to thin layer chromatography; and "RT" refers to room temperature.

5

Preparation 1

Preparation of [3S,4aR,6S,8aR]-6-methylidene-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.



A slurry of methyltriphenylphosphonium bromide (12.4 g, 34.6 mmol) in THF (25 mL) was cooled to -10 to -12°C under an atmosphere of nitrogen and treated with sodium hexamethyldisilazide (35 mL of a 1M solution in THF) via syringe over 6 to 8 minutes with stirring. The reaction mixture was then stirred for 20 minutes at -10 to -12°C and added via cannula over 3-4 minutes to [3S,4aR,6S,8aR]-6-oxo-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (10.0 g, 26.6 mmol), [which had previously been treated with sodium hexamethyldisilazide (27 mL of 1 M solution in THF) at $0-3^{\circ}\text{C}$ and stirred for 10 minutes] dissolved in DMF (20 mL) and cooled to $0-3^{\circ}\text{C}$ under an atmosphere of nitrogen. This was followed by a THF (3 mL) rinse of the flask holding the Wittig reagent which was also added to the reaction mixture. The reaction mixture was then allowed to stir for 5 minutes at $0-3^{\circ}\text{C}$, was then allowed to warm to room temperature, and stirred for an additional 3 hours. Ethyl acetate (100 mL) and water (50 mL) were added with stirring and then the layers were separated. The organic layer was extracted with water (50 mL) and the combined aqueous portions were washed with methylene chloride (5 X 75 mL). The aqueous was then treated with 6M HCl (15 mL) and extracted with methylene chloride (3 X 50 mL). The organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the title compound (6.59 g, 98%) as a yellow oil.

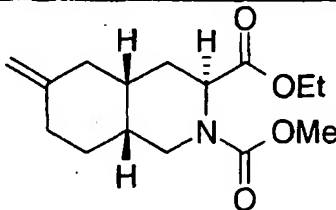
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Alternative synthesis of [3S,4aR,6S,8aR]-6-methylidene-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.

A slurry of [3S,4aR,6S,8aR]-6-oxo-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (50.0 g, 0.133 mol, 1.0 equiv) and methyltriphenylphosphonium bromide (66.4 g, 0.186 mol, 1.4 equiv) in THF (150 mL) and DMF (25 mL) was stirred mechanically under an atmosphere of nitrogen and cooled to -10 °C. Potassium *tert*-butoxide solution (187 mL of 1.7 M in THF, 0.319 mol, 2.4 equiv) was added dropwise over a 10 minute period. A mild exotherm throughout this addition resulted in an increase of the reaction temperature to 6 °C. The slurry was allowed to warm to room temperature and stirred thus for 2.5 hours (complete by TLC at this time). Reaction was partitioned between water (250 mL) and EtOAc (250 mL) and the layers were separated. The organic phase was extracted with water (2 X 100 mL) and the aqueous portions were combined and washed with dichloromethane (5 X 300 mL). The aqueous solution was made acidic by addition of 6 M HCl solution (50 mL) and extracted with dichloromethane (3 X 150 mL). These last three organic extracts were combined, dried with sodium sulfate and concentrated under reduced pressure to provide the title compound as a yellow film (36.17 g). Estimated potency of the product by proton NMR was 89 wt% (remainder residual solvents) for a corrected yield of 32.2 g (95.6%).

Preparation 2

Preparation of [3S,4aR,6S,8aR]-Ethyl-6-methylidene-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



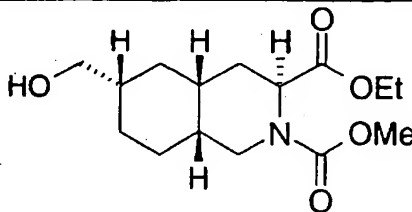
[3S,4aR,6S,8aR]-6-methylidene-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (6.59 g, 26.0 mmol, prepared in preparation 1) was dissolved in acetonitrile (26 mL) and treated with triethylamine (7.25 mL, 52 mmol) and bromoethane (5.82 mL, 78

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mmol). The reaction was heated at 50°C for about 3 hours, cooled and partitioned between 50:50 ethyl acetate/heptane (100 ml) and 1N HCL (75 mL). The organic phase was isolated and washed with water (3 X 30 mL), saturated sodium bicarbonate (30 mL), brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the crude title compound as an amber oil. This crude material was dissolved in 10% ethyl acetate/heptane (15 mL) and applied to a plug of silica gel (10 g in 10% ethyl acetate/heptane). The plug was eluted with 10% ethyl acetate/heptane (10 mL), 15% ethyl acetate/heptane (15 mL), and 25% ethyl acetate/heptane (90 mL). The eluents were combined and concentrated under vacuum to provide the purified titled compound (6.84 g, 91%) as a colorless oil.

Preparation 3

15 Preparation of [3S,4aR,6S,8aR]-Ethyl-6-(hydroxymethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



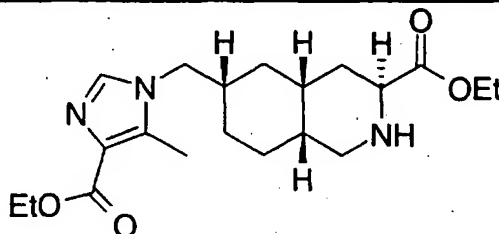
[3S,4aR,6S,8aR]-Ethyl-6-methylidene-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (51.1 g, 181 mmol, prepared in preparation 2) was dissolved in THF (250 mL) and cooled to about -15°C under an atmosphere of nitrogen with stirring. A 1M solution of BH₃•THF (121 mL, 121 mmol, in THF) was added dropwise over 5-7 minutes and the reaction mixture was stirred for about 2 hours at -10 to -12°C. The reaction was then slowly treated with ethanol (32 mL, exotherm) over 7-9 minutes and then treated slowly with 30% H₂O₂ (91 mL, exotherm) over 15 minutes. The reaction mixture was allowed to warm to room temperature over 45 minutes and then partitioned between ethyl acetate (450 mL) and 50% saturated sodium chloride solution (700 mL). The aqueous layer was extracted with ethyl acetate (250 mL) and the combined organics were washed with 5% sodium bisulfite solution (400 mL), brine (200 mL), dried over anhydrous sodium sulfate, filtered, and

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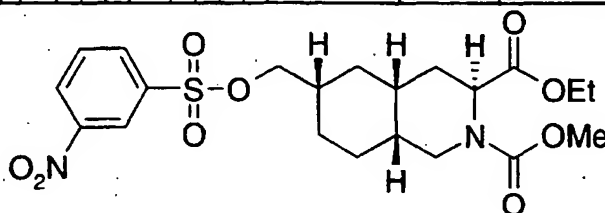
concentrated under vacuum to provide the title compound (54.41 g) as a colorless oil.

Example 1

- 5 Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-5-methyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



- Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((3-nitrophenylsulfonyloxy)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

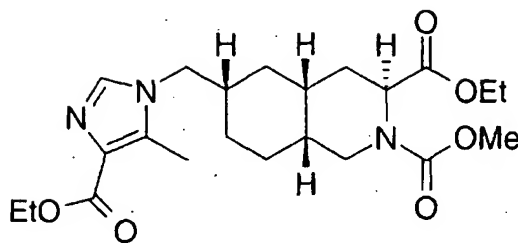


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- Scheme I, step A: To a solution of 1.0 g of [3S,4aR,6S,8aR]-ethyl-6-(hydroxymethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate and 0.78 g of 3-nitrobenzenesulphonyl chloride in 25ml methylene chloride at 5°C was added 1.4 ml of triethylamine dropwise. The reaction was allowed to warm to room temperature and stirred for 18 h. The crude reaction solution was washed with water, 1N hydrochloric acid, saturated aqueous sodium bicarbonate and brine, dried (sodium sulfate), filtered and evaporated. The resulting viscous oil was dried under vacuum at 50°C to provide 1.1 g of the intermediate title compound: MS m/z 486 ($m^+ + 1$);
- 15 400-MHz ^1H NMR (CDCl_3) δ 1.15 (m, 2H), 1.2 (t, 3H), 1.4-1.6 (m, 5H), 1.85 (m, 3H), 2.1 (m, 1H), 3.25 (m, 1H), 3.35 (dd, 1H), 3.65 (s, 3H), 3.95 (m, 2H), 4.15 (q, 2H), 4.35 (t, 1H), 7.75 (t, 1H), 8.2 (d, 1H), 8.5 (d, 1H), 8.7 (s, 1H).
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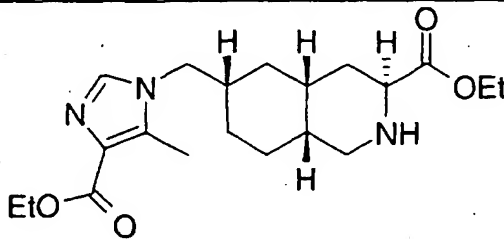
- Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-5-methyl-1H-imidazol-1-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.
- 25

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Scheme I, step B: Sodium hydride (0.24 g, 1.2 eq) was washed with hexanes (3 x 10 ml) and suspended in dry THF (10 ml). To this was added a solution of 0.848 g of ethyl 4-methyl-5-imidazolecarboxylate in THF (5 ml) dropwise. The reaction mixture was stirred at 20°C for 1.5 h and DMF (10 ml) was added. To the resulting solution was slowly added a solution of 2.43 g of [3S,4aR,6S,8aR]-ethyl-6-((3-nitrophenylsulfonyloxy)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate in THF (10 ml). The reaction was stirred at ambient temperature over night under N₂. The reaction was quenched with saturated aqueous sodium bicarbonate. The resulting white solid was removed by filtration and the filtrate was extracted with ethyl acetate (3 x 10 ml). The combined organic extract was washed with brine, dried (MgSO₄), filtered, and evaporated to a light brown oil. The crude product was chromatographed over silica gel eluting with ethyl acetate to give 1.09 g of the intermediate title compound: MS m/z: 456.3 (m⁺+1); 400-MHz ¹H NMR (CDCl₃) δ 7.62 (s, 1H), 4.42-4.33 (m, 3H), 4.20-4.16 (m, 2H), 3.84-3.72 (m, 2H), 3.70 (s, 3H), 3.48-3.42 (dd, 2H), 3.40-3.28 (t, 1H), 2.50 (s, 3H), 2.24-2.16 (m, 1H), 1.95-1.88 (m, 1H), 1.86-1.80 (m, 2H), 1.80-1.75 (m, 1H), 1.67-1.60 (m, 2H), 1.56-1.43 (m, 2H), 1.42-1.36 (t, 3H), 1.26-1.22 (t, 3H), 1.20-1.08 (m, 2H).

Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-5-methyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



Scheme I, step C: To a solution of 0.435 g of [3S,4aR,6S,8aR]-ethyl-6-((4-ethoxycarbonyl-5-methyl-1H-imidazol-1-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate in dry dichloromethane (30 ml) at 20°C was added 0.71 ml of trimethylsilyl iodide dropwise under N₂. The reaction was stirred at 20°C for 18 h. The reaction was quenched by addition of EtOH (5 ml) and concentrated to dryness. The residue was dissolved in ethyl acetate and saturated aqueous sodium bicarbonate. The two phases were separated. The aqueous layer was extracted with EtOAc (3 x 10 ml). The combined organic extracts were washed with brine, dried (sodium sulfate), filtered, and evaporated. The resulting residue chromatographed over silica gel eluting with 1% methanol in chloroform to give 0.205 g of the intermediate title compound: MS m/z: 378.3 (m⁺+1); 400-MHz ¹H NMR (CDCl₃) δ 7.39 (s, 1H), 7.25 (s, 1 H), 4.37-4.32 (q, 2H), 4.19-4.13 (q, 2H), 3.74-3.72 (m, 3H), 3.49-3.426(dd, 1H), 3.40-3.28 (t, 1H), 2.90-2.75 (dd, 1H), 2.52 (s, 3H), 2.19-2.09 (m, 3H), 1.92-1.88 (m, 2H), 1.75-1.72 (m, 2H), 1.63-1.59 (m, 1H), 1.48-1.59 (m, 1H), 1.44-1.36 (t, 3H), 1.27-1.23 (t, 3H), 1.03-0.88 (m, 2H).

Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-5-methyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.

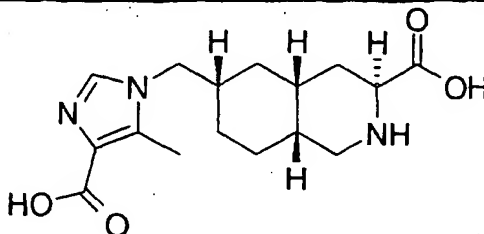
To a solution of 0.325 g of [3S,4aR,6S,8aR]-ethyl-6-((4-ethoxycarbonyl-5-methyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate in dry ethyl acetate (5 mL) at 20°C was added 3.4 ml of a 1.0M solution of HCl in diethyl ether. The resulting precipitate was collected through filtration and vacuum dried at 50°C to yield 0.214 g of the final title compound, [3S,4aR,6S,8aR]-ethyl-6-((4-ethoxycarbonyl-5-methyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride: MS m/z: 378.3 (m⁺+1-HCl); ¹H NMR 400 MHz (CD₃OD) δ 9.12 (s, 1H), 4.44-4.38 (m, 2H), 4.27-4.22 (m, 2H), 4.16-4.09 (m, 3H), 3.38-3.32 (t, 1H), 3.06 (br s, 2 H), 3.08-3.02 (dd, 1H), 2.6 2 (s, 3H), 2.17-2.02 (m, 2H), 1.98-1.90 (m, 3H), 1.74-1.64

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(m, 2H), 1.63-1.59 (m, 1H), 1.46-1.33 (m, 5H), 1.31-1.25 (t, 3H), 1.23-1.08 (m, 1H).

Example 2

- 5 Preparation of [3S,4aR,6S,8aR]-6-((4-carboxylic acid-5-methyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.



- Scheme I, step D: To a solution of 0.267 g of [3S,4aR,6S,8aR]-ethyl-6-((4-ethoxycarbonyl-5-methyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate in methanol at 20°C was added 7.1 ml of a 1.0 M aqueous solution of lithium hydroxide. The resulting mixture was stirred for 18 h. Upon completion, the reaction was neutralized to pH=6 with 1.0N HCl and evaporated to a white solid. The crude product was purified by strong cation exchange chromatography eluting with 50% methanol in water followed by 2.0M ammonium hydroxide in methanol to provide 0.226 g of the title compound: MS m/z: 322.2 ($m^+ + 1$); 400-MHz ^1H NMR (CD_3OD) δ 7.60 (br s, 1H), 3.94-3.82 (m, 2H), 3.79-3.73(d, 1H), 3.32-3.24 (d, 1H), 3.22-3.18 (t, 1H), 2.89-2.82 (d, 1H), 2.50 (m, 3H), 2.18-2.01 (m, 2H), 1.96-1.90 (m, 1H), 1.86-1.73 (m, 2H), 1.70-1.62 (br. s, 2H), 1.58-1.42 (m, 1H), 1.42-1.30 (br. s, 2H), 1.03-0.88 (m, 1H) (note that the two COOH and one NH protons were exchanged with the solvent).

- 25 Preparation of [3S,4aR,6S,8aR]-6-((4-Carboxylic acid-5-methyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

- To a solution of 0.223 g of [3S,4aR,6S,8aR]-6-((4-carboxylic acid-5-methyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid in dry ethyl acetate (5 mL) at 20°C was added 2.1 ml of a 1.0M solution of HCl in diethyl ether. The resulting precipitate was collected through

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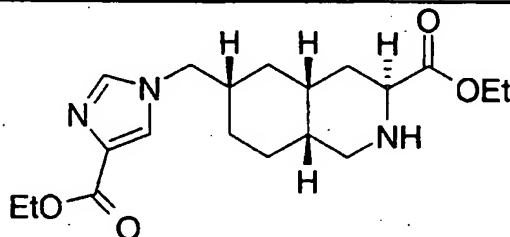
filtration and vacuum dried at 50°C to yield 0.21 g of [3S,4aR,6S,8aR]-6-((4-carboxylic acid-5-methyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride:

MS m/z: 322.4 ($m^+ + 1\text{-HCl}$).

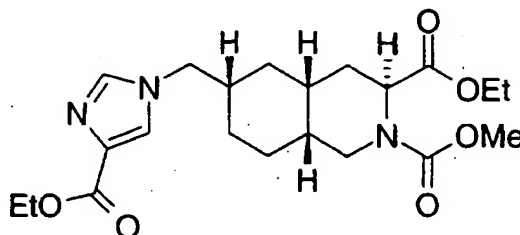
- 5 400-MHz ^1H NMR (D_2O) δ 0.90 (m, 1H), 1.15 (m, 3H), 1.40 (m, 2H), 1.62-1.95 (m, 4H), 2.25 (3H), 2.85 (dd, 1H), 2.98 (t, 1H), 3.55 (dd, 1H), 3.82 (d, 2H), 4.20 (q, 1H), 8.5 (s, 1H).

Example 3

- 10 Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



- 15 Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



- Scheme I, step B: In 100 mL anhydrous dimethylformamide was dissolved 6.81 g of ethyl-4-imidazolecarboxylate. At room temperature, 1.94 g of NaH were added and the reaction was allowed to stir for 1 hour. To the reaction
- 20 was added 23.56 g of [3S,4aR,6S,8aR]-ethyl-6-((3-nitrophenylsulfonyloxy)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dissolved in 100 mL dimethylformamide. The reaction mixture was stirred at ambient temperature overnight and evaporated to dryness. The residue was redissolved in ethyl acetate and
- 25 washed with saturated sodium bicarbonate solution. The layers were separated

and the aqueous was extracted with three portions of ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was chromatographed over silica gel eluting with 0% to 2% methanol in chloroform to give 8.04 g of the intermediate title compound: MS m/z: 422.1 ($m^+ + 1$);

^1H NMR (400 MHz, CDCl_3) δ 7.53 (s, 1H), 7.4 (s, 1H), 4.39-4.3 (m, 3H), 4.2-4.1 (m, 2H), 3.85-3.75 (m, 2H), 3.7 (s, 3H), 3.42-3.38 (dd, 1H), 3.35-3.25 (t, 1H), 2.2-2.1 (m, 1H), 1.95-1.9 (m, 1H), 1.89-1.75 (m, 2H), 1.7-1.65 (m, 1H), 1.64-1.55 (m, 1H), 1.54-1.4 (m, 3H), 1.38-1.3 (t, 3H), 1.25-1.2 (t, 3H), 1.2-1.0 (m, 2H).

Alternative preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

Scheme I, step B: Ethyl-4-imidazolecarboxylate (486 mg, 3.46 mmol) was added in portions to a slurry of sodium hydride (146 mg of a 60% mineral oil dispersion, 3.64 mmol) in THF (3.0 mL). The resulting tea-colored solution was stirred at room temperature for 55 minutes. It was then treated with [3S,4aR,6S,8aR]-ethyl-6-((3-nitrophenylsulfonyloxy)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (1.68 g, 3.46 mmol, prepared in example 1) dissolved in THF (3.5 mL), and the reaction mixture was stirred overnight at room temperature. The reaction was then partitioned between dichloromethane (6.5 mL) and water (6.5 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (5 mL). The organic extract and organic layer were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the crude title compound. This material was purified flash chromatography (5% to 10% ethanol/toluene containing 0.5% dimethylamine, 34 g silica gel) to provide the purified intermediate title compound (1.16 g, 79%) as a colorless film.

Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

Scheme I, step C: To a solution of 0.90 g of [3S,4aR,6S,8aR]-ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-2-(methoxycarbonyl)-

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1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate in 20 ml of methylene chloride was added 1.5 ml trimethylsilyl iodide. The reaction was stirred at room temperature for six hours, quenched with excess absolute ethanol and evaporated to dryness. The residue was purified by strong cation exchange chromatography eluting with 10-50% methanol in chloroform followed by 50% 2M ammonia/methanol in chloroform to provide the final title compound, [3S,4aR,6S,8aR]-ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

10 Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.

[3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate was dissolved in ethyl acetate and excess 1M HCl in diethyl ether was added. The resulting white precipitate was filtered and vacuum dried at 50°C for 18hr to give 0.62 g of [3S,4aR,6S,8aR]-ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride: MS m/z : 364 ($m^+ + 1$); Analysis calculated for $C_{19}H_{29}N_3O_4 \cdot 2HCl \cdot H_2O$: C, 50.20; H, 6.89; N, 9.25. Found: C, 50.51; H, 6.86; N, 9.25.

25 Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate citrate (1:1 molar salt complex).

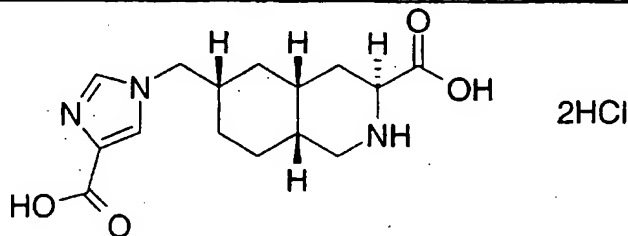
[3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (511 mg, 1.04 mmol) was dissolved in 2-propanol (3.0 mL) and treated with a solution of citric acid (270 mg, 1.04 mmol, dissolved in 2.0 mL 2-propanol). The resulting slurry was heated to effect solution and seeded with authentic salt. The mixture was cooled slowly to room temperature with stirring and then cooled further in an ice-water bath. [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-

1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate citrate was collected by filtration as a colorless crystalline solid (717 mg, 92%).

5 Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate methanesulfonate.

The methanesulfonic acid salt of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate is prepared in a manner analogous to the
10 procedures described above from one equivalent of methanesulfonic acid and one equivalent of [3S,4aR,6S,8aR]-Ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate in ethyl acetate.

15 Example 4
Preparation of [3S,4aR,6S,8aR]-6-((4-Carboxylic acid-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

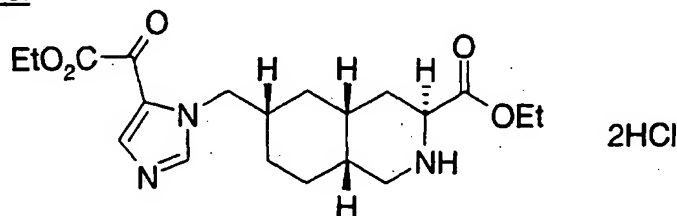


Scheme I, step D: A solution of 0.80 g of [3S,4aR,6S,8aR]-ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (prepared in example 3) in 10 mL of 5N HCl
20 was heated at 70°C for 18 h. After cooling to 20°C, the solution was evaporated and the resulting residue vacuum dried at 50°C to give 0.526 g of the title compound: MS m/z: 308 ($m^+ + 1$); Analysis calculated for $C_{15}H_{21}N_3O_4 \cdot 2HCl \cdot H_2O$:
25 C, 45.2; H, 6.34; N, 10.54. Found: C, 45.72; H, 6.30; N, 10.75.

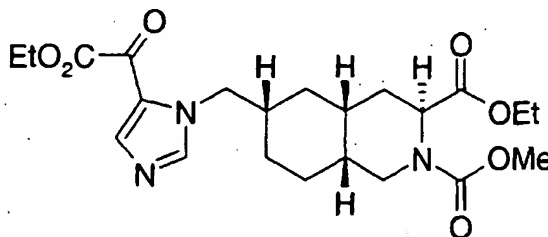
-35-

Example 5

Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((5-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.



Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((5-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



- 10 Scheme I, step B: Following the identical procedure set forth in example 3, chromatographic separation provided 0.76 g of the title compound: MS m/z: 422.2 ($m^+ + 1$);
- 400 MHz ^1H NMR (CDCl_3) δ 7.8-7.7 (bs, 1H), 7.7-7.65 (bs, 1H), 4.35-4.3 (t, 1H), 4.3-4.2 (m, 2H), 4.2-4.1 (m, 4H), 3.7-3.6 (s, 3H), 3.45-3.35 (dd, 1H), 3.3-3.2 (t, 1H), 2.2-2.1 (m, 1H), 1.95-1.85 (m, 3H), 1.7-1.6 (m, 1H), 1.6-1.5 (m, 1H), 1.5-1.35 (m, 3H), 1.35-1.3 (t, 3H), 1.25-1.2 (t, 3H), 1.2-1.05 (m, 2H).
- 15

Preparation of final title compound.

- 20 Scheme I, step C: In a manner analogous to the procedure described in example 3, [3S,4aR,6S,8aR]-ethyl-6-((5-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride was obtained from [3S,4aR,6S,8aR]-ethyl-6-((5-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate: MS m/z: 364($m^+ + 1$);

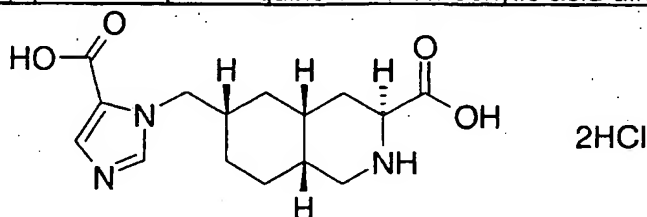
-36-

Analysis calculated for $C_{19}H_{29}N_3O_4 \cdot 2HCl \cdot H_2O$: C, 50.20; H, 6.89; N, 9.25.

Found: C, 50.43; H, 7.17; N, 9.12.

Example 6

- 5 Preparation of [3S,4aR,6S,8aR]-6-((5-Carboxylic acid-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



- Scheme I, step D: In a manner analogous to the procedure described in example 4, the title compound was obtained from [3S,4aR,6S,8aR]-ethyl-6-((5-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride (prepared in example 5):
 10 MS m/z: 308.1 ($m^+ + 1$);

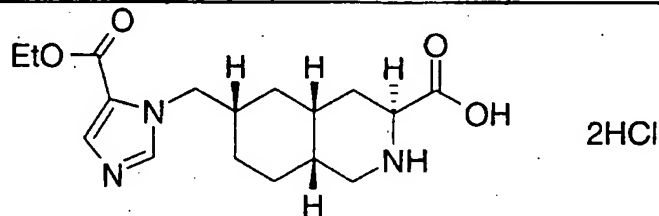
Analysis calculated for $C_{15}H_{21}N_3O_4 \cdot 2HCl \cdot H_2O$: C, 45.2; H, 6.34; N, 10.54.

Found: C, 46.1; H, 6.18; N, 10.50.

15

Example 7

- Preparation of [3S,4aR,6S,8aR]-6-((5-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



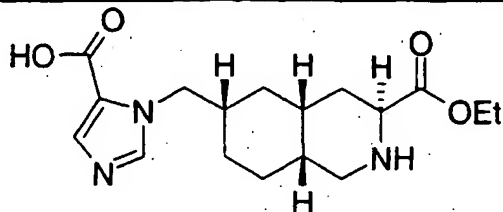
- 20 Scheme I, step E: A solution of 0.20 g of [3S,4aR,6S,8aR]-ethyl-6-((5-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride (prepared in example 5) in 10 mL of 5N HCl was heated at 50°C for three hours and then at room temperature for 18 h. The solution was evaporated and vacuum dried at 50°C to
 25 give 0.173 g of the title compound: MS m/z: 336.2 ($m^+ + 1$). Analysis calculated

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for $C_{17}H_{25}N_3O_4 \cdot 2HCl \cdot H_2O$: C, 47.9; H, 6.9; N, 9.85. Found: C, 48.11; H, 7.66; N, 9.99.

Example 8

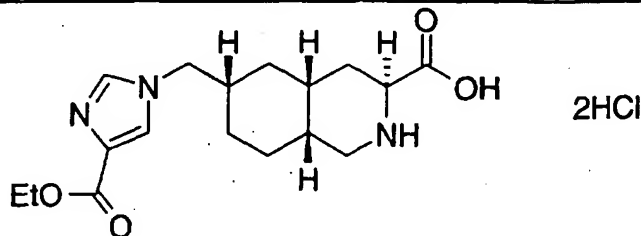
- 5 Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((5-carboxylic acid-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



- Scheme I, step F: To a suspension of 1.2 g of [3S,4aR,6S,8aR]-6-((5-carboxylic acid-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride (prepared in example 6) in absolute ethanol was added 9.5 mL 1M HCl in diethyl ether. The reaction was heated at reflux overnight and evaporated. The residue was purified by strong cation exchange chromatography eluting with methanol followed by 0.8M ammonia in methanol. The purified material was recrystallized from isopropyl alcohol to give 0.320 g of the title compound: MS m/z : 334.2 (m^{-1}); Analysis calculated for $C_{17}H_{25}N_3O_4 \cdot H_2O$: C, 57.7; H, 7.15; N, 11.8. Found: C, 57.04; H, 7.34; N, 11.59.

Example 9

- 20 Preparation of [3S,4aR,6S,8aR]-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



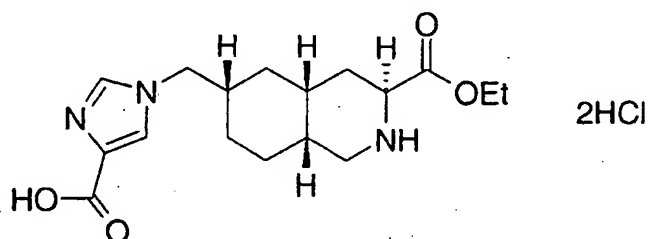
- Scheme I, step E: A solution of 0.20 g of [3S,4aR,6S,8aR]-ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (prepared in example 3) in 10 mL of 5N HCl was heated at 50°C for three hours and then at room temperature for 18 h. The

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solution was evaporated and the resulting residue was chromatographed over C18 modified silica gel eluting with acetonitrile in aqueous 0.1% HCl to give 0.105 g of the title compound: MS m/z: 336 ($m^+ + 1$); Analysis calculated for $C_{17}H_{25}N_3O_4 \cdot HCl \cdot 1.5H_2O$: C, 51.2; H, 7.35; N, 10.55. Found: C, 51.33; H, 7.04; N, 10.62.

Example 10

Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-carboxylic acid-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.

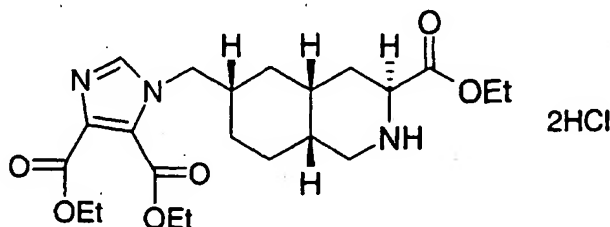


Scheme I, step F: To a suspension of 0.2 g of [3S,4aR,6S,8aR]-6-((4-Carboxylic acid-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride (prepared in example 4) in absolute ethanol was added 9.5 mL 1M HCl in diethyl ether. The reaction was heated at reflux overnight, cooled and evaporated to dryness. The resulting residue was chromatographed over C18 modified silica gel eluting with acetonitrile in aqueous 0.1% HCl to give 0.165 g of the title compound: MS m/z: 336.2 ($m^+ + 1$); 400 MHz 1H NMR ($CDCl_3$) δ 8.4 (s, 1H), 7.9 (s, 1H), 4.3-4.2 (m, 2H), 4.1-4.0 (m, 3H), 3.25-3.2 (m, 1H), 3.1-3.0 (dd, 1H), 2.15-2.0 (m, 3H), 2.0-1.9 (m, 2H), 1.75-1.6 (m, 2H), 1.5-1.3 (m, 3H), 1.3-1.2 (t, 3H), 1.15-1.0 (m, 1H).

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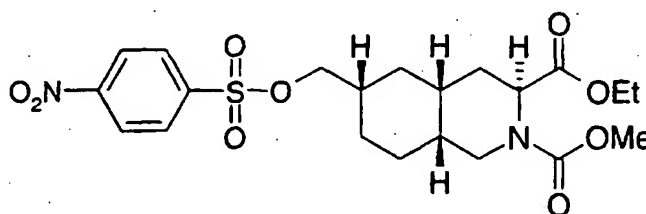
Example 11

Preparation of [3S,4aR,6S,8aR]-Ethyl 6-([4,5-Bis(ethoxycarbonyl)-1H-imidazol-1-yl]methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride:



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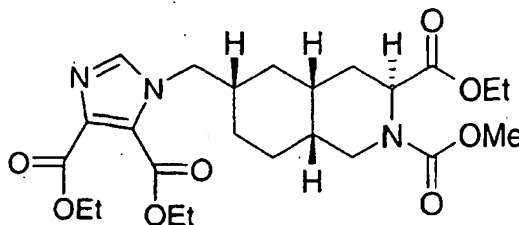
Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4-nitrophenylsulfonyloxy)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



10 Scheme I, step A: A solution of [3S,4aR,6S,8aR]-ethyl-6-(hydroxymethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (8.50 g, 0.0284 mol), triethylamine (8.62 g, 0.852 mol), 4-nitrobenzenesulfonyl chloride (6.49 g, 0.0284 mol), and dichloromethane (121 mL) was stirred at ambient temperature and monitored by tlc (ethyl acetate / hexane 1:1 / I₂ stain).
 15 After three hours, additional 4-nitrobenzenesulfonyl chloride (0.63 g, 0.00284 mol) was added and the reaction stirred one additional hour at ambient temperature. The reaction mixture was concentrated to dryness. The residue was dissolved in ethyl acetate (121 mL) and filtered to remove triethylamine hydrochloride. The filtrate was washed with 1N hydrochloric acid solution (2 x
 20 100 mL), saturated sodium bicarbonate solution (2 x 100 mL), and saturated sodium chloride solution (1 x 100 mL). The organic layer was dried using sodium sulfate, filtered, and concentrated to give 13.42 g (98%) of the intermediate title compound as an orange oil.

25 ¹H nmr (CDCl₃): δ 1.15-1.29 (m, 5H), 1.44-1.69 (m, 5H), 1.78-1.94 (m, 3H), 2.08-2.17 (dt, 1H), 3.29-3.45 (m, 2H), 3.69 (s, 3H), 3.91-4.03 (m, 2H), 4.14-4.21 (q, 2H), 4.36-4.40 (t, 1H), 8.06-8.10 (dd, 2H), 8.38-8.41 (dd, 2H).

Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4,5-bis-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



- 5 Scheme I, step B: A solution of [3S,4aR,6S,8aR]-ethyl-6-((4-nitrophenylsulfonyloxy)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (13.42 grams, 0.0277 mol), diethyl 4,5-imidazolecarboxylate [Y. S. Rhee, R. A. Jones, *J. Am. Chem. Soc.* **1990**, 112, 8174.] (11.70 g, 0.0554 mol), and *N,N*-dimethylformamide (83 mL) was heated
- 10 for three hours at 60°C until complete as determined by tlc (hexane / ethyl acetate, 1:1). The reaction was cooled, diluted with saturated sodium bicarbonate (300 mL) and extracted with ethyl acetate (4 x 100 mL). The combined extracts were washed with 5% lithium chloride solution, dried using sodium sulfate, and concentrated to dryness. The residue was purified using
- 15 Biotage Flash 40M (dichloromethane / methanol, 49:1) to give 10.87 g (79%) of the intermediate title compound as an amber oil.
- ¹H nmr (CDCl₃): δ 1.03-1.11 (q, 2H), 1.17-1.22 (t, 3H), 1.26-1.35 (m, 6H), 1.35-1.46 (m, 3H), 1.51-1.59 (m, 1H), 1.59-1.66 (m, 1H), 1.72-1.78 (m, 2H), 1.78-1.90 (t, 1H), 2.05-2.14 (m, 1H), 3.21-3.33 (m, 1H), 3.33-3.41 (dd, 1H), 3.64 (s, 3H),
- 20 3.97-4.08 (m, 2H), 4.08-4.15 (q, 2H), 4.26-4.35 (m, 5H), 7.42 (s, 1H). MS (FIA) m/z 494.3 ([M+H]⁺)

Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4,5-bis-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

- 25 Scheme I, step C: A solution of [3S,4aR,6S,8aR]-ethyl-6-((4,5-bis-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (10.55 g, 0.02138 mol), iodotrimethylsilane (21.39 g, 0.1069 mol), and dichloromethane (428 mL)

was stirred for 16 hours at ambient temperature until complete as determined by tlc (ethyl acetate / hexane, 2:1). The reaction mixture was concentrated to approximately 200 mL, ethanol (100 mL) was added and the resulting solution concentrated to a yellow foam. The residue was dissolved in methanol (190 mL) and stirred for 30 minutes with Amberlyst 15 resin (50 g). The resin was filtered and washed with methanol (100 mL). The product was eluted from the Amberlyst resin with 2N ammonia in methanol (2 x 100 mL). The filtrate was concentrated to an oil. The residue was purified by Biotage Flash 40M (dichloromethane / methanol, 19:1) to give 4.72 g of the free base of the final title compound, [3S,4aR,6S,8aR]-ethyl-6-((4,5-bis-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4,5-bis-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.

[3S,4aR,6S,8aR]-Ethyl-6-((4,5-bis-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate was dissolved in ethyl acetate (50 mL) and a solution of 1.86M hydrochloric acid in ethyl acetate (11.65 mL, 0.0217 mol) was added giving a sticky solid. The reaction mixture was concentrated to dryness. The residue was dissolved in dichloromethane (10 mL) and added dropwise to diethyl ether (150 mL) causing the precipitation of 5.09 g (47%) of [3S,4aR,6S,8aR]-Ethyl-6-((4,5-bis-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride; mp 99-101°C.

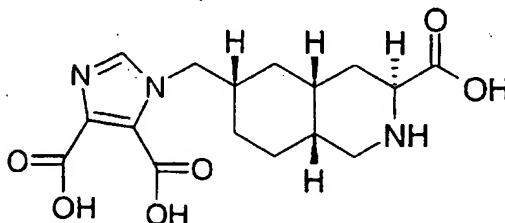
¹H nmr (DMSO-d₆): δ 0.87-1.0 (q, 1H), 1.09-1.15 (d, 1H), 1.15-1.26 (m, 10H), 1.38-1.52 (m, 2H), 1.52-1.58 (d, 1H), 1.65-1.76 (s, broad, 1H), 1.76-1.89 (m, 3H), 2.04-2.13 (d, 1H), 2.47 (s, 1H), 2.91-2.99 (d, 1H), 2.99-3.08 (q, 1H), 3.94-4.09 (m, 3H), 4.16-4.31 (m, 6H), 7.92 (s, 1H), 9.18-9.29 (d, 1H), 9.63-9.72 (d, 1H).

MS (FIA) m/z 436.3 ([M+H]⁺).

Anal. Calcd. for C₂₂H₃₅N₃O₆Cl₂: C: 51.97; H: 6.94; N: 8.26. Found: C: 51.82; H: 7.02; N: 8.18.

Example 12

Preparation of [3S,4aR,6S,8aR]-Ethyl-6-((4,5-dicarboxylic acid -1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.



Scheme I, step D: To a solution of 0.15 g of [3S,4aR,6S,8aR]-Ethyl-6-((4,5-bis-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (prepared in example 11) in methanol at 20°C was added 6.4 ml of a 1.0 M aqueous solution of lithium hydroxide. The resulting mixture was stirred for 18 h. Upon completion, the reaction was acidified to pH 4 with 1N HCl and evaporated to dryness. The crude product was purified by strong cation exchange chromatography eluting with 50% methanol in water followed by 10% pyridine in methanol / water (1:1) to provide [3S,4aR,6S,8aR]-ethyl-6-((4,5-dicarboxylic acid -1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

Preparation of [3S,4aR,6S,8aR]-ethyl-6-((4,5-dicarboxylic acid -1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.

[3S,4aR,6S,8aR]-Ethyl-6-((4,5-dicarboxylic acid -1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate was dissolved in water, treated with 1.5 ml of 1N HCl and evaporated to provide 0.65 g of [3S,4aR,6S,8aR]-ethyl-6-((4,5-dicarboxylic acid -1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride: MS m/z: 350.2 ([m-H]⁺); 400MHz ¹H NMR (CD₃OD) δ 1.05 (bs, 1H), 1.25-1.67 (m, 5H), 1.85-2.17 (m, 5H), 3.00 (dd, 1H), 3.15 (d, 1H), 3.72 (d, 1H), 4.35 (dd, 2H), 7.75 (s, 1H).

To establish that the iGluR₅ receptor subtype is mediating neurogenic protein extravasation, a functional characteristic of migraine, the binding affinity of the compounds of formula I to the iGluR₅ receptor is first measured using standard methods. For example, the activity of compounds acting at the iGluR₅ receptor can be determined by radiolabelled ligand binding studies at the cloned and expressed human iGluR₅ receptor (Korczak et al., 1994, Recept. Channels 3; 41-49), and by whole cell voltage clamp electrophysiological recordings of currents in acutely isolated rat dorsal root ganglion neurons (Bleakman et al., 1996, Mol. Pharmacol. 49; 581-585). The selectivity of compounds acting at the iGluR₅ receptor subtype can then be determined by comparing antagonist activity at the iGluR₅ receptor with antagonist activity at other AMPA and kainate receptors. Methods useful for such comparison studies include: receptor-ligand binding studies and whole-cell voltage clamp electrophysiological recordings of functional activity at human GluR₁, GluR₂, GluR₃ and GluR₄ receptors (Fletcher et al., 1995, Recept. Channels 3; 21-31); receptor-ligand binding studies and whole-cell voltage clamp electrophysiological recordings of functional activity at human GluR₆ receptors (Hoo et al., Recept. Channels 2; 327-338); and whole-cell voltage clamp electrophysiological recordings of functional activity at AMPA receptors in acutely isolated cerebellar Purkinje neurons (Bleakman et al., 1996, Mol. Pharmacol. 49; 581-585) and other tissues expressing AMPA receptors (Fletcher and Lodge, 1996, Pharmacol. Ther. 70; 65-89).

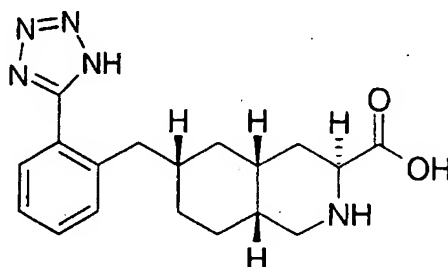
iGluR₅ antagonist binding affinity profiles

Cell lines (HEK293 cells) stably transfected with human iGluR receptors are employed. Displacement of ³[H] AMPA by increasing concentrations of antagonist is measured on iGluR₁, iGluR₂, iGluR₃, and iGluR₄ expressing cells, while displacement of ³[H] kainate (KA) is measured on iGluR₅, iGluR₆, iGluR₇, and KA2-expressing cells. As an indicia of selectivity, the ratio of binding affinity to the iGluR₂ AMPA receptor subtype, versus the binding affinity to iGluR₅ kainate receptor subtype, is also determined. As noted above, the compounds

of the present invention display a surprisingly selective binding affinity for the iGluR₅ receptor. More specifically, the compounds of the present invention exhibit at least a 20 fold greater binding affinity for the iGluR₅ receptor than for iGluR₂ receptor.

5

In comparison, the binding affinity of:



which is example 4 as disclosed in United States Patents No. 5,446,051, displays only a 5 fold selectivity for the iGluR₅ receptor over the iGluR₂ receptor.

10

The ability of the compounds to treat migraine may be demonstrated as described in United States Patent Nos. 5,817,671 and 5,792,763 and as described in J. Neurosci. Methods, 81(1,2) 19-24 (1998). For example, the following animal model is employed to determine the ability of each of the compounds of formula I to inhibit protein extravasation, an exemplary functional assay of the neuronal mechanism of migraine. The results obtained from this model are provided in Table I below.

15

Animal Model of Dural Protein Extravasation

20

Harlan Sprague-Dawley rats (225-325 g) or guinea pigs from Charles River Laboratories (225-325 g) are anesthetized with sodium pentobarbital intraperitoneally (65 mg/kg or 45 mg/kg respectively) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -3.5 mm for rats or -4.0 mm for guinea pigs. Following a midline sagittal scalp incision, two pairs of bilateral holes are drilled through the skull (6 mm posteriorly, 2.0 and 4.0 mm laterally in rats; 4 mm posteriorly and 3.2 and 5.2 mm laterally in guinea pigs, all

25

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coordinates referenced to bregma). Pairs of stainless steel stimulating electrodes, insulated except at the tips (Rhodes Medical Systems, Inc.), are lowered through the holes in both hemispheres to a depth of 9 mm (rats) or 10.5 mm (guinea pigs) from dura.

5 The femoral vein is exposed and a dose of the test compound is injected intravenously (i.v.) at a dosing volume of 1ml/Kg or, in the alternative, test compound is administered orally (p.o) via gavage at a volume of 2.0ml/Kg . Approximately 7 minutes post i.v. injection, a 50 mg/Kg dose of Evans Blue, a fluorescent dye, is also injected intravenously. The Evans Blue complexes with
10 proteins in the blood and functions as a marker for protein extravasation. Exactly 10 minutes post-injection of the test compound, the left trigeminal ganglion is stimulated for 3 minutes at a current intensity of 1.0 mA (5 Hz, 4 msec duration) with a Model 273 potentiostat/ galvanostat (EG&G Princeton Applied Research).

 Fifteen minutes following stimulation, the animals are killed and
15 exsanguinated with 20 mL of saline. The top of the skull is removed to facilitate the collection of the dural membranes. The membrane samples are removed from both hemispheres, rinsed with water, and spread flat on microscopic slides. Once dried, the tissues are coverslipped with a 70% glycerol/water solution.

 A fluorescence microscope (Zeiss) equipped with a grating monochromator
20 and a spectrophotometer is used to quantify the amount of Evans Blue dye in each sample. An excitation wavelength of approximately 535 nm is utilized and the emission intensity at 600 nm was determined. The microscope is equipped with a motorized stage and also interfaced with a personal computer. This facilitates the computer-controlled movement of the stage with fluorescence
25 measurements at 25 points (500 nm steps) on each dural sample. The mean and standard deviation of the measurements are determined by the computer.

 The extravasation induced by the electrical stimulation of the trigeminal ganglion is an ipsilateral effect (i.e. occurs only on the side of the dura in which the trigeminal ganglion is stimulated). This allows the other (unstimulated) half of
30 the dura to be used as a control. The ratio of the amount of extravasation in the dura from the stimulated side, over the amount of extravasation in the unstimulated side, is calculated. Control animals dosed with only with saline,

yield a ratio of approximately 2.0 in rats and approximately 1.8 in guinea pigs. In contrast, a compound which effectively prevents the extravasation in the dura from the stimulated side would yield a ratio of approximately 1.0. A dose-response curve is generated for the compound and the dose that inhibits the extravasation by 50% (ID₅₀) or 100% (ID₁₀₀) is approximated. The ID₁₀₀ for the compound of example 3 given orally is 0.3 ng/Kg.

As used herein the term "patient" refers to a mammal, such a mouse, gerbil, guinea pig, rat, dog, monkey, or human. It is understood, however, that the preferred patient is a human.

As used herein, the terms "treating" or "to treat" each mean to alleviate symptoms, eliminate the causation of resultant symptoms either on a temporary or permanent basis, and to prevent, slow the appearance, or reverse the progression or severity of resultant symptoms of the named disorder. As such, the methods of this invention encompass both therapeutic and prophylactic administration.

As used herein the term "effective amount" refers to the amount or dose of the compound, upon single or multiple dose administration to the patient, which provides the desired effect in the patient under diagnosis or treatment.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose of compound administered, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the degree of involvement or the severity of the migraine involved; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of each compound used in the present method of treatment. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg.

In effecting treatment of a patient afflicted with a condition, disease or disorder described herein, a compound of formula I can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, compounds of formula I can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the disease state to be treated, the stage of the disease, and other relevant circumstances.

The selective iGluR₅ antagonists for use according to the methods of the present invention may be a single compound or a combination of compounds capable of functioning as a selective iGluR₅ receptor antagonist. For example, it may be a combination of a compound capable of functioning as an antagonist at the iGluR₅ receptor and one or more other glutamate receptors, in combination with one or more compounds capable of blocking its actions at the iGluR₂ receptor. It is understood, however, that the selective iGluR₅ antagonist for use in the methods of the present invention, is preferably a single compound.

Pharmaceutical compositions

Oral administration is a preferred route of administering the compounds employed in the present invention whether administered alone, or as a combination of compounds capable of acting as a selective iGluR₅ receptor antagonist. Oral administration, however, is not the only route, nor even the only preferred route. Other preferred routes of administration include transdermal, percutaneous, intravenous, intramuscular, intranasal, buccal, or intrarectal routes. Where the selective iGluR₅ receptor antagonist is administered as a combination of compounds, one of the compounds may be administered by one route, such as oral, and the other may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal, buccal, or intrarectal route, as particular circumstances require. The route of administration may be varied in

any way, limited by the physical properties of the compounds and the convenience of the patient and the caregiver.

The compounds employed in the present invention may be administered as pharmaceutical compositions and, therefore, pharmaceutical compositions incorporating said compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally administered pharmaceutical compositions are particularly preferred. Such pharmaceutical compositions contain an effective amount of a selective iGluR₅ receptor antagonist, which effective amount is related to the daily dose of the compound to be administered. Each dosage unit may contain the daily dose of a given compound, or may contain a fraction of the daily dose, such as one-half or one-third of the dose. The amount of each compound to be contained in each dosage unit depends on the identity of the particular compound chosen for the therapy, and other factors such as the indication for which it is given. The pharmaceutical compositions of the present invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing well known procedures.

Compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg of each compound individually or in a single unit dosage form, more preferably about 5 to about 300 mg (for example 25 mg). The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for a patient, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient.

The inert ingredients and manner of formulation of the pharmaceutical compositions are conventional. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on

the desired doses and the type of composition to be used. The amount of the compound, however, is best defined as the "effective amount", that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the compounds employed in the present invention do not depend on the nature of the composition, hence, the compositions are chosen and formulated solely for convenience and economy.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starches, powdered cellulose especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours, and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

A lubricant is often necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algin and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange
5 resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid
10 environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate.

When it is desired to administer the compound as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may
15 be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially
20 dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

25 The following table provides an illustrative list of formulations suitable for use with the compounds employed in the present invention. The following is provided only to illustrate the invention and should not be interpreted as limiting the present invention in any way.

-51-

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
5	
10	
Active Ingredient	250
Starch, dried	200
Magnesium stearate	<u>10</u>
Total	460 mg

15 The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

20 A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
25	
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
30 Stearic acid	<u>5</u>
Total	665 mg

35 The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

5		Weight %
	Active Ingredient	0.25
	Ethanol	29.75
10	Propellant 22 (Chlorodifluoromethane)	<u>70.00</u>
	Total	100.00

15 The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

20

Formulation 4

Tablets each containing 60 mg of active ingredient are made as follows:

25	Active Ingredient	60 mg
	Starch	45 mg
	Microcrystalline cellulose	35 mg
	Polyvinylpyrrolidone	4 mg
	Sodium carboxymethyl starch	4.5 mg
30	Magnesium stearate	0.5 mg
	Talc	<u>1 mg</u>
	Total	150 mg

35

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a
40 No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then

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added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

5 Capsules each containing 80 mg medicament are made as follows:

	Active Ingredient	80 mg
	Starch	59 mg
10	Microcrystalline cellulose	59 mg
	Magnesium stearate	<u>2 mg</u>
	Total	200 mg

15

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 sieve, and filled into hard gelatin capsules in 200 mg quantities.

20

Formulation 6

Suppositories each containing 225 mg of active ingredient may be made as follows:

25	Active Ingredient	225 mg
	Saturated fatty acid glycerides	<u>2,000 mg</u>
	Total	2,225 mg

30

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions each containing 50 mg of medicament per 5 ml dose are made as follows:

5		
	Active Ingredient	50 mg
	Sodium carboxymethyl cellulose	50 mg
	Syrup	1.25 ml
	Benzoic acid solution	0.10 ml
10	Flavor	q.v.
	Color	q.v.
	Purified water to total	5 ml

15 The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

20

Formulation 8

An intravenous formulation may be prepared as follows:

25	Active Ingredient	100 mg
	Mannitol	100 mg
	5 N Sodium hydroxide	200 ml
	Purified water to total	5 ml

30

As with any group of structurally related compounds which possess a particular generic utility, certain groups and configurations are preferred for compounds of formula I.

35 With respect to substituent W, compounds wherein W is hydrogen, methyl, or CO₂H are preferred, with hydrogen being most preferred.

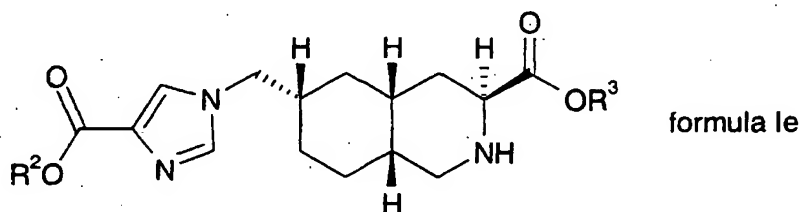
With respect to substituent X, compounds wherein X is hydrogen, methyl, or CO₂H are preferred, with CO₂H being most preferred.

With respect to R^1 , compounds wherein R^1 is hydrogen or C_1 - C_{20} alkyl are preferred, compounds wherein R^1 is C_1 - C_4 alkyl are most preferred, and compounds wherein R^1 is methyl or ethyl are most especially preferred.

With respect to R^2 , compounds wherein R^2 is hydrogen or C_1 - C_{20} alkyl are preferred, compounds wherein R^2 is C_1 - C_4 alkyl are most preferred, and compounds wherein R^2 is methyl or ethyl are most especially preferred.

With respect to R^3 , compounds wherein R^3 is hydrogen, C_1 - C_{20} alkyl are preferred, compounds wherein R^3 is C_1 - C_4 alkyl are most preferred, and compounds wherein R^3 is methyl or ethyl are most especially preferred.

In particular, compounds of formula Ie:

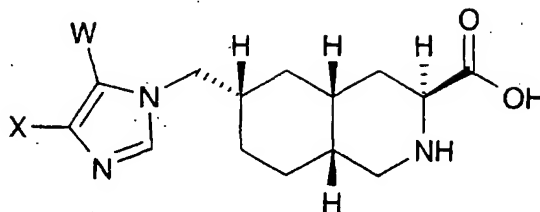


wherein R^2 and R^3 are each independently hydrogen, methyl or ethyl, are especially preferred.

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We claim:

1. A compound of the formula:



- 5 wherein

W represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂H, or CO₂H; and
X represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂H, or CO₂H;
with the proviso that at least one of W or X must be other than hydrogen;
or a prodrug or a pharmaceutically acceptable salt thereof.

10

2. The compound according to claim 1 wherein W represents hydrogen.

3. The compound according to claim 1 wherein X represents hydrogen.

15

4. The compound according to claim 3 wherein W represents CO₂H.

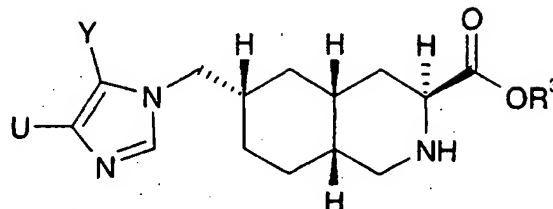
5. A compound which is [3S,4aR,6S,8aR]-6-((4-carboxylic acid-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof.

20

6. A compound according to claim 5 wherein the pharmaceutically acceptable salt is the dihydrochloride.

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7. A compound of the formula:



wherein

- 5 Y represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂R¹, or CO₂R¹;
 U represents hydrogen, C₁-C₄ alkyl, -CH₂CO₂R², or CO₂R²; and
 R¹, R² and R³ each independently represent hydrogen, C₁-C₂₀ alkyl, C₂-C₆
 alkenyl, C₁-C₆ alkylaryl, C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl, C₁-C₆ alkyl-N,N-C₁-C₆
 dialkylamine, C₁-C₆ alkyl-pyrrolidine, C₁-C₆ alkyl-piperidine, or C₁-C₆ alkyl-
 10 morpholine;
 or a pharmaceutically acceptable salt thereof,
 with the proviso that at least one of Y or U is other than hydrogen or C₁-C₄ alkyl,
 and with the further proviso that at least one of R¹, R² or R³ is other than
 hydrogen.
- 15 8. The compound according to claim 7 wherein U is CO₂R².
9. The compound according to claim 8 wherein R² and R³ are each
 independently C₁-C₂₀ alkyl.
- 20 10. The compound according to claim 9 wherein R² and R³ are each
 independently C₁-C₄ alkyl.
11. The compound according to claim 7 wherein U is hydrogen.
- 25 12. The compound according to claim 11 wherein Y is CO₂R¹.

13. The compound according to claim 12 wherein R¹ and R³ are each independently C₁-C₂₀ alkyl.

14. The compound according to claim 13 wherein R¹ and R³ are each
5 independently C₁-C₄ alkyl.

15. The compound according to claim 14 wherein R¹ and R³ are each independently methyl or ethyl.

10 16. A compound which is [3S,4aR,6S,8aR]-ethyl-6-((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate or a pharmaceutically acceptable salt thereof.

17. A compound according to claim 16 which is [3S,4aR,6S,8aR]-ethyl-6-
15 ((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.

18. A compound according to claim 16 which is [3S,4aR,6S,8aR]-ethyl-6-
20 ((4-ethoxycarbonyl-1H-imidazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate citrate.

19. A method of treating migraine which comprises administering to a patient an effective amount of a compound according to claim 1.

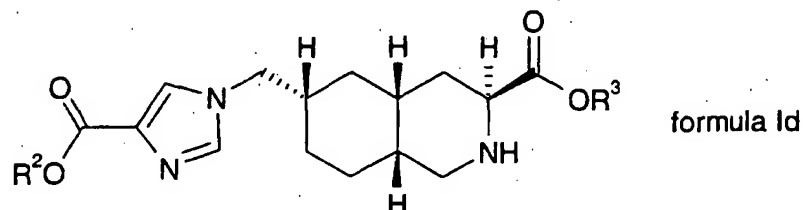
25 20. A pharmaceutical composition comprising an effective amount of a compound according any of Claims 1 to 18 in combination with a pharmaceutically acceptable carrier, diluent or excipient.

21. The use of a compound according to claim 1 for the manufacture of a
30 medicament for the treatment of migraine.

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22. The use of a compound according to claim 1 for the treatment of migraine.

23. A process for preparing a compound of formula Id:

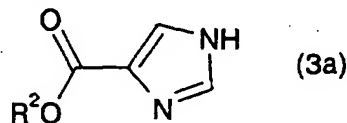


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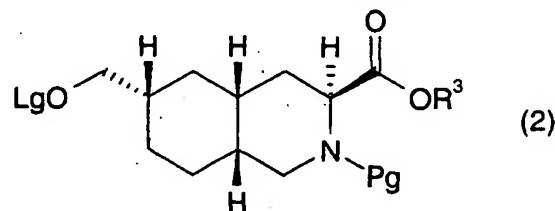
wherein

R^2 and R^3 each independently represent C_1 - C_{20} alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkylaryl, C_1 - C_6 alkyl(C_3 - C_{10})cycloalkyl, C_1 - C_6 alkyl-N,N- C_1 - C_6 dialkylamine, C_1 - C_6 alkyl-pyrrolidine, C_1 - C_6 alkyl-piperidine, or C_1 - C_6 alkyl-morpholine;

10 comprising combining a compound of structure (3a):



wherein R^2 is defined as above, with a suitable base in a suitable solvent, followed by addition of a compound of structure (2):



15 wherein R^3 is defined as above, Pg is a suitable nitrogen protecting group, and OLg is a suitable leaving group, followed by removal of the nitrogen protecting group.

INTERNATIONAL SEARCH REPORT

International Application No.

PC1/US 00/32450

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/06 A61K31/47 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 446 051 A (ORNSTEIN) 29 August 1995 (1995-08-29) cited in the application column 14, line 31 - column 16, line 49; claims; examples	1-23
A	US 5 356 902 A (ORNSTEIN) 18 October 1994 (1994-10-18) column 16, line 4 - line 63; claims; examples	1-23
A	US 5 675 008 A (BERTSCH ET.AL.) 7 October 1997 (1997-10-07) column 35, line 55 - column 36, line 44; claims; examples	1-23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

3 April 2001

Date of mailing of the international search report

20.04.01

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INTERNATIONAL SEARCH REPORT

International Application No

PCI/US 00/32450

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>P. L. ORNSTEIN ET. AL.: "Structure-Activity Studies of 6-Substituted Decahydroisoquinoline- 3-carboxylic Acid AMPA Receptor Antagonists. " JOURNAL OF MEDICINAL CHEMISTRY , vol. 39, no. 11, 24 May 1996 (1996-05-24), pages 2232-44, XP002164592 page 2238, column 2 -page 2241, column 1; tables 1-4</p>	1-23
E	<p>WO 01 01972 A (ELI LILLY & CO.) 11 January 2001 (2001-01-11) claims; examples</p>	1-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/32450

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19 and 22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/32450

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5446051 A	29-08-1995	NONE	
US 5356902 A	18-10-1994	US 5527810 A	18-06-1996
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WO 0101972 A	11-01-2001	NONE	

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